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(54) MDC proteins and DNAs encoding the same.

(57) The present invention provide a gene present in a commonly deleted region of a chromosome in breast and ovarian cancers and encoding a novel protein, the protein ("MDC protein") encoded by the gene, a method for the diagnosis of cancer by using an antibody combinable to the protein, and others.

A detailed genetic map of human chromosome 17 was constructed to analyze the chromosome in breast and ovarian cancer tissues, and a gene encoding a novel protein was cloned and its structure was determined. As a result of gene analysis using DNA probes derived from the gene, a gene mutation was confirmed in breast cancer tissues. Moreover, a transformant carrying a plasmid containing the gene was grown to obtain the MDC protein. Furthermore, a monoclonal antibody was prepared by using the protein as antigen.

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Background of the Invention

Field of the Invention

The present invention relates to MDC proteins, DNAs encoding the same, and gene analysis methods using the DNAs. The present invention can be utilized in such fields as medical treatment and diagnosis.

Description of the Related Art

The opinion that mutations in cellular proteins play an important role in the onset of cancer has been known for long. Recent advancement in genetic engineering enables analysis of gene mutations in tumor cells, and has brought about a marked progress in the field of cancer research.

Up to this time, the analysis and identification of oncogenes have made such progress that the number thereof has amounted to several tens. On the other hand, attention has been focused on tumor suppressor genes for these several years. The tumor suppressor genes which have been discovered thus far include the Rb gene for retinoblastoma (Friend, S.H. et al., Proc. Natl. Acad. Sci. USA, 84, 9095, 1987), the p53 gene (Lane, D.P. et al., Nature, 278, 261, 1979) and the APC gene (Kenneth, W.K. et al., Science, 253, 661, 1991) for colorectal tumor, the WT1 gene for Wilms' tumor (Call, K.M. et al., Cell, 60, 509, 1990), and the like. In the case of the p53 gene, some families are known to be inheriting mutations in the gene ["Li-Fraumeni syndrome" (Makin, D. et al., Science, 250, 1233, 1990; Srivastava, S. et al., Nature, 348, 747, 1990)]. Moreover, it is becoming increasingly clear that defects in multiple genes, and not in a single gene, contribute to the progression of the malignant phenotype of cancer, and it is believed that there exist much more unidentified oncogenes and tumor suppressor genes. The discovery and elucidation of them are expected by not only investigators and clinicians, but also common people in all the world.

Breast cancer is classified into hereditary (familial) breast cancer and nonhereditary (sporadic) breast cancer, and hereditary breast cancer is classified into early-onset and late-onset diseases according to the age of onset. It has been revealed by linkage analyses that, at least early-onset familial, breast cancer linked to a very small region on chromosome 17 (Hall, J.M. et al., Science, 250, 1684-1689, 1990). Moreover, it has been shown that hereditary ovarian cancer is also linked to the same region (Narod, S.A. et al., Lancet, 338, 82-83, 1991).

Accordingly, it is believed that a tumor suppressor gene is present in this region and protein deficiency or mutation induced by an allelic deletion or mutation of the gene is one of the causes of breast and ovarian cancers.

It is believed that in the onset of common (sporadic) breast cancer as well, the occurence of an acquired mutation or allelic deletion of the gene in this region results in protein mutation or deficiency and this causes the transformation of a normal cell to a breast cancer (Sato et al., Cancer Res., 51, 5794-5799, 1991). Consequently, isolation of the causative gene present in this region and identification of the protein encoded by the gene are expected as an urgent problem to not only physicians and investigators in all the world, but also common people, particularly women in Europe and America where there are numerous patients with breast cancer.

The present invention provides novel proteins involved in breast and ovarian cancers, DNAs encoding them, and methods for the testing and diagnosis of cancer by using them.

The present inventors disclose a novel gene encoding a 524-amino acid protein which was isolated from chromosomal region 17q21.3 where a tumor suppressor gene(s) for breast and ovarian cancers is thought to be present (Nature genetics, 5, 151-157, 1993; this paper is refered in Nature genetics, 5, No. 2, 101-102, 1993).

Disclosure of the Invention

Brief Description of the Drawings

Fig. 1 is a diagram showing the positions on chromosome 17 to which 342 cosmid clones hybridize. Clone names are designated by clone numbers alone.

Fig. 2 is a diagram showing partial deletions on chromosome 17q in ovarian cancers. Solid circles represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two commonly deleted regions are designated by sidelines.

Fig. 3 is a diagram showing partial deletions on chromosome 17q in breast cancers. Solid circles represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two

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commonly deleted regions are designated by sidelines.

Fig. 4 is a diagram showing the process starting with markers on chromosome 17q21.3 and leading to the isolation of the gene, as well as the regions where genomic rearrangements occurred in tumor tissues (hatched boxes). Clone names are designated by clone numbers alone.

Figs. 5-7 are diagrams showing the detection of genomic rearrangements in breast cancers by Southern-blot analysis. Symbols N and T represent DNAs from normal tissue and tumor tissue, respectively.

Fig. 8 is a graph showing a working curve for determining the concentration of the MDC protein by ELISA using a monoclonal antibody and a rabbit polyclonal antibody.

Summary of the Invention

The present inventors constructed a multitude of cosmid clones having DNA fragments of human chromosome 17 introduced thereinto. Then, each of the multitude of cosmid clones was localized throughout the chromosome by fluorescent in-situ hybridization (FISH; Inazawa et al., Genomics, 10, 1075-1078, 1991). The cosmid clones (cosmid markers), localized on the chromosome, enabled construction of a high-resolution physical map of human chromosome 17. The clone names of the cosmids as probes, i.e., the probe names, their detailed map positions and diagrammatical summary of the mapping are shown in Tables 1-3 and Fig. 1, respectively. In Fig. 1, clone names are designated by clone numbers alone.

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Table 1

No.	Probe name	Locus symbol	Chromosomal localization	No.	Probe name	Locus symbol	Chromosomal localization
1	cCI17-1		17q21.1	67	cCI17-501		17q21.3
2	cCI17-7		17q22	68	cCI17-502		17p11.2
3	cCI17-11		17p11.2	69	cCI17-504		17q24
4	cCI17-24		17q21.1-q21.2	70	cCI17-505	D17S544	17p12-p11.1
5	cCI17-25		17q12	71	cCI17-506	D17S545	17q21
6	cCI17-28		17q21.3	72	cCI17-507		17q21.3
7	cCI17-32		17q11.2	73	cCI17-508	D17S546	17q25.1-q25.2
8	cCI17-35		17q21.3	74	cCI17-509		17q24
9	cCI17-44		17q23.1	75	cCI17-510		17q23
10	cCI17-50		17q23.1	76	cCI17-511		17q25.1-q25.2
11	cCI17-57		17q21	77	cCI17-513	D17S548	17q11.2
12	cCI17-63		17q21.3	78	cCI17-514		17q25.1
13	cCI17-90		17q12-q21.1	79	cCI17-515		17q22
14	cCI17-95		17q23.1	80	cCI17-516	D17S550	17q25.1
15	cCI17-96		17q21.3	81	cCI17-517		17q21.3
16	cCI17-97		17q21.31	82	cCI17-518		17q25.3
17	cCI17-315	D17S521	17q25.1-q25.2	83	cCI17-519	D17S551	17q25.2-q25.3
18	cCI17-316		17q12-q21.1	84	cCI17-520		17q11.2
19	cCI17-317		17q11.2	85	cCI17-521		17q25.1-q25.2
20	cCI17-321		Centromere	86	cCI17-523		17q22
21	cCI17-403		17q21.2-q21.3	87	cCI17-524		17q21.1-q21.2
22	cCI17-412		17q11.2	88	cCI17-525		17p13.1
23	cCI17-415		17q21.1-q21.2	89	cCI17-526		17q11.2-q12
24	cCI17-422		17q22	90	cCI17-527		17q21.3
25	cCI17-425		17q11.2	91	cCI17-528		17q22
26	cCI17-428		17q23.1	92	cCI17-529	D17S552	17q25.1-q25.2
27	cCI17-451		17q21.1-q21.2	93	cCI17-530		17q23
28	cCI17-452	D17S524	17q25	94	cCI17-532		17p11.2
29	cCI17-453	D17S525	17p13	95	cCI17-533		17q21.3
30	cCI17-454	D17S526	17q23	96	cCI17-535		17q12-q21.1
31	cCI17-456	D17S527	17q23.1-q23.2	97	cCI17-536		17p11.2
32	cCI17-457		17q11.2	98	cCI17-539		17q21.3
33	cCI17-458	D17S528	17q21.1-q21.2	99	cCI17-540		17q25
34	cCI17-460	D17S529	17q11.2	100	cCI17-541		17q21.3
35	cCI17-462		17q23	101	cCI17-542		17q21.3
36	cCI17-463		17q21	102	cCI17-543		17q11.2-q12
37	cCI17-464		17q24.3-q25.1	103	cCI17-544		17q25.1
38	cCI17-465	D17S531	17q25.1-q25.2	104	cCI17-545		17q25.1
39	cCI17-466		17q25.1-q25.2	105	cCI17-546		17q24.3-q25.1
40	cCI17-467		17q25	106	cCI17-547		17q21.3
41	cCI17-468	D17S532	17q11.2	107	cCI17-548		17q23
42	cCI17-469	D17S533	17q25.2-q25.3	108	cCI17-549		17q25.3
43	cCI17-471		17p13.3-p13.2	109	cCI17-550		17q23
44	cCI17-473	D17S534	17q11.2	110	cCI17-551		17q25.1-q25.2
45	cCI17-475	D17S535	17q11.2	111	cCI17-552		17q12
46	cCI17-477		17q21.3	112	cCI17-553		17q23
47	cCI17-479		17q21.3	113	cCI17-554		17q25.1
48	cCI17-480		17q25.1-q25.2	114	cCI17-557		17q25.1-q25.2
49	cCI17-482	D17S536	17q11.2	115	cCI17-559		17q24.3-q25.1
50	cCI17-483		17p13	116	cCI17-560		17q25.1-q25.2
51	cCI17-484	D17S537	17p13.1	117	cCI17-561		17q25
52	cCI17-485		17q12	118	cCI17-562		17q11.2
53	cCI17-486		17q25.1	119	cCI17-563		17q25.1
54	cCI17-487	D17S538	17q25.1	120	cCI17-564		17q25.1
55	cCI17-488	D17S539	17p13.2-p13.1	121	cCI17-565		17q23
56	cCI17-489	D17S540	17q23	122	cCI17-567		17q21.3
57	cCI17-490		17q11.2	123	cCI17-568		17q25
58	cCI17-491		17p13.1	124	cCI17-569		17q12
59	cCI17-492	D17S542	17q11.2	125	cCI17-570		17q11.1
60	cCI17-493		17q25.1-q25.2	126	cCI17-571		17p13
61	cCI17-494		17q22	127	cCI17-572		17q25.1
62	cCI17-495		17q25	128	cCI17-573		17q25.3
63	cCI17-497		17q11.2	129	cCI17-574		17q12-q21.2
64	cCI17-498		17p11.2	130	cCI17-576		17q21.1-q21.2
65	cCI17-499		17q21.1-q21.2	131	cCI17-577		17q25.1
66	cCI17-500		17p.12	132	cCI17-578		17q11.2-q12

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Table 2

No.	Probe name	Locus symbol	Chromosomal localization	No.	Probe name	Locus symbol	Chromosomal localization
133	cCI17-579		17q25.1	198	cCI17-652		17q22
134	cCI17-581		17q11.2	199	cCI17-653		17q22
135	cCI17-582		17q21.3	200	cCI17-654		17p13
136	cCI17-583		17q12-q21.1	201	cCI17-655		17q23
137	cCI17-584		17q21.3	202	cCI17-656		17q25.1
138	cCI17-586		17p13	203	cCI17-657		17p13
139	cCI17-587		17p13	204	cCI17-658		17q21.3
140	cCI17-588		17p13.1	205	cCI17-659		17q25.1
141	cCI17-590		17q12	206	cCI17-660		17q25.1
142	cCI17-591		17q24	207	cCI17-662		17p12
143	cCI17-592		17q21.3	208	cCI17-663		17q25.1
144	cCI17-593		17q25.1-q25.2	209	cCI17-664		17q25.1-q25.2
145	cCI17-594		17q25.2-q25.3	210	cCI17-665		17q23
146	cCI17-595		17q25.1-q25.2	211	cCI17-666		17q23.1
147	cCI17-596		17q11.2	212	cCI17-667		17q24
148	cCI17-597		17q25.3	213	cCI17-668		17q22
149	cCI17-598		17q12-q21.1	214	cCI17-669		17p13
150	cCI17-599		17q12	215	cCI17-670		17q21.3
151	cCI17-600		17q23	216	cCI17-671		17q11.2
152	cCI17-601		17q21.1-q21.2	217	cCI17-672		17q25.1-q25.2
153	cCI17-602		17q11.2-q12	218	cCI17-673		17q12-q21.1
154	cCI17-603		17p11.2	219	cCI17-674		17q21.3
155	cCI17-604		17q23	220	cCI17-675		17q21.3
156	cCI17-605		17q21.1-q21.2	221	cCI17-676		17q23
157	cCI17-606		17p13	222	cCI17-677		17q12-q21.1
158	cCI17-607		17q25	223	cCI17-678		17q23
159	cCI17-608		17p11.2	224	cCI17-679		17q23.1
160	cCI17-609		17q21.3	225	cCI17-680		17p13
161	cCI17-610		17q12-q21.1	226	cCI17-681		17p11.1-p11.2
162	cCI17-611		17q22	227	cCI17-683		17q11.2
163	cCI17-612		17q21.3	228	cCI17-684		17q25.1-q25.2
164	cCI17-613		17q25.1	229	cCI17-685		17p13
165	cCI17-614		17q21.3	230	cCI17-687		17q12
166	cCI17-615		17q21.1	231	cCI17-688		17p11.2
167	cCI17-616		17q25.1	232	cCI17-690		17q11.2-q12
168	cCI17-617		17q21.3	233	cCI17-691		17q25.1
169	cCI17-618		17q23.1	234	cCI17-692		17q23
170	cCI17-619		17q21.3	235	cCI17-693		17p11.2
171	cCI17-621		17q25.1-q25.2	236	cCI17-694		17p11.2
172	cCI17-622		17q12	237	cCI17-695		17p11.2
173	cCI17-623		17q25.1-q25.2	238	cCI17-696		17q23.3
174	cCI17-624		17p13	239	cCI17-697		17q25
175	cCI17-625		17q23	240	cCI17-698		17q11.2
176	cCI17-626		17q23	241	cCI17-699		17q23
177	cCI17-627		17p13	242	cCI17-700		17q23
178	cCI17-628		17q23	243	cCI17-701		17q21.3
179	cCI17-630		17q11.2	244	cCI17-702		17q25.2-q25.3
180	cCI17-631		17p11.2	245	cCI17-703		17p13
181	cCI17-662		17q22	246	cCI17-704		17q23
182	cCI17-633		17q12	247	cCI17-705	D17S554	17p11.2
183	cCI17-634		17q21.3	248	cCI17-706	D17S555	17q12
184	cCI17-636		17p13	249	cCI17-707	D17S556	17q25.1-q25.2
185	cCI17-637		17q12	250	cCI17-708		17p13
186	cCI17-638		17p11.2	251	cCI17-709		17p12
187	cCI17-639		17q12	252	cCI17-710	D17S557	17q25.3
188	cCI17-640		17q11.2	253	cCI17-711		17q32.1
189	cCI17-641		17q25.1	254	cCI17-712	D17S558	17p11.2
190	cCI17-642		17q12-q21.1	255	cCI17-713	D17S559	17p13
191	cCI17-643		17q21.3	256	cCI17-714	D17S560	17q25.3
192	cCI17-644		17q23	257	cCI17-715		17q21.3
193	cCI17-645		17p13	258	cCI17-716	D17S561	17p13
194	cCI17-646		17p13	259	cCI17-717		17p13
195	cCI17-647		17q25.1-q25.2	260	cCI17-719		17q25
196	cCI17-650		17q12	261	cCI17-721		17q23
197	cCI17-651		17q25.1	262	cCI17-722	D17S563	17q25.2-q25.3

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Table 3

No.	Probe name	Locus symbol	Chromosomal localization	No.	Probe name	Locus symbol	Chromosomal localization
263	cCI17-723		17p13	304	cCI17-834		17q11.2-q12
264	cCI17-724	D17S564	17p11.2	305	cCI17-835		17q21.3
265	cCI17-726		17q25	306	cCI17-841		17p12
266	cCI17-727	D17S566	17p13	307	cCI17-1005		17q21.3
267	cCI17-728	D17S567	17p12	308	cCI17-1008		17q21.3
268	cCI17-729	D17S568	17q11.2	309	cCI17-1016		17q23.1
269	cCI17-730		17q21.3	310	cCI17-1018		17q21.2-21.3
270	cCI17-732	D17S570	17p13.2	311	cCI17-1019		17q23.1
271	cCI17-733		17q25.1	312	cCI17-1024		17q12
272	cCI17-735	D17S572	17q25.3	313	cCI17-1029		17q11.2
273	cCI17-736	D17S573	17q21.3	314	cCI17-1030		17q22
274	cCI17-737	D17S557	17q25.2-q25.3	315	cCI17-1031		17q11.2
275	cCI17-739	D17S575	17q25.1	316	cCI17-1032		17q23.1-23.2
276	cCI17-741		17q25.3	317	cCI17-1049		17q21.3
277	cCI17-742		17q25	318	cCI17-1055		17q21.3
278	cCI17-743		17q23.3	319	cCI17-1059		17q21.1-q21.2
279	cCI17-744		17q23	320	cCI17-1063		17q12
280	cCI17-745	D17S577	17p13	321	cCI17-1073		17q11.2
281	cCI17-801		17q11.2-q12	322	cCI17-1079		17q12
282	cCI17-802		17p11.2	323	cCI17-1082		17q22
283	cCI17-808		17q25.1-q25.2	324	cCI17-1094		17q21.1
284	cCI17-809		17q23	325	cCI17-1101		17q12
285	cCI17-810		17p13.2-p13.1	326	cCI17-1103		17q11.2
286	cCI17-812		17q25.1	327	cCI17-1106		17q11.2
287	cCI17-813		17q23	328	cCI17-1702		17q21.1-q21.2
288	cCI17-814		17p11.2	329	cCI17-1705		17q21.2-q21.3
289	cCI17-815		17q24	330	cCI17-1706		17q21.1-q21.2
290	cCI17-816		17q23	331	cCI17-1707		17q21.2-q21.3
291	cCI17-817		17q23	332	cCI17-1709		17q12
292	cCI17-818		17p11.2	333	cCI17-1710		17q21.3
293	cCI17-820		17q12	334	cCI17-1711		17q12
294	cCI17-821		17p13	335	cCI17-1715		17q12
295	cCI17-822		17q11.1	336	cCI17-1717		17q21.3
296	cCI17-823		17q12	337	cCI17-1719		17q11.2
297	cCI17-825		17p11.2	338	cCI17-1720		17q24.3-q25.1
298	cCI17-826		17q11.2	339	cCI17-1722		17q23
299	cCI17-827		17p11.2	340	cCI17-1723		17q21.3
300	cCI17-828		17p11.2	341	cCI17-1724		17q11.2
301	cCI17-831		17q25.1-q25.2	342	cCI17-1725		17q21.1
302	cCI17-832		17p11.2	343	pCMM86		17q23
303	cCI17-833		17q23				

From among these markers, ones exhibiting restriction fragment length polymorphism (RFLP) in which the lengths of restriction fragments vary with the individual, namely RFLP markers, were selected. The selected marker clones, the restriction enzymes used, and the particular lengths of several fragments detected thereby are shown in Tables 4-6.

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Table 4

No.	Probe name	Locus symbol	Enzyme	Allele size (frequency)	Chromosomal localization
2	cCI17-7	D17S860	PvuII	3.0 kb(0.33) 1.8+1.2 kb(0.67)	
16	cCI17-97	D17S861	PstI	8.2 kb(0.92) 4.7+3.5 kb(0.08)	17q21.3
17	cCI17-315	D17S521	TaqI	2.0 kb(0.67) 1.8 kb(0.33)	17q25.1-q25.2
18	cCI17-316	D17S862	MspI	3.1 kb(0.33) 2.7 kb(0.67)	17q12-q21.1
19	cCI17-317	D17S522	TaqI 2.6-3.9 kb 4 alleles VNTR,60% heterozygosity also polymorphic with MspI,PstI,PvuII		17q11.2
29	cCI17-453	D17S525	BglII 5.8-7.5 kb 4 alleles VNTR,50% heterozygosity also polymorphic with EcoRI,TaqI,PstI,PvuII,MapI		17p13
42	cCI17-469	D17S533	MspI 2.0-2.6 kb 5 alleles VNTR,83% heterozygosity also polymorphic with EcoRI,TaqI,PvuII		17q25.2-q25.3
54	cCI17-487	D17S536	EcoRI	5.8 kb(0.75) 3.3 kb(0.25)	17q25.1
56	cCI17-489	D17S540	MspI	3.3 kb(0.25) 2.1 kb(0.50)	17q23
			TaqI	1.5 kb(0.50) 1.35 kb(0.50)	
			PvuII	1.2 kb(0.50) 0.7 kb(0.50)	
58	cCI17-491	D17S863	TaqI	3.6 kb(0.75) 3.3 kb(0.25)	17p13.1
59	cCI17-492	D17S542	BglII	2.1 kb(0.40) 1.4 kb(0.60)	17q11.2
61	cCI17-494	D17S865	EcoRI	10.3 kb(0.92) 7.8 kb(0.008)	
70	cCI17-505	D17S544	MspI	3.1 kb(0.58) 3.0 kb(0.42)	17p12-p11.1
			TaqI	4.1 kb(0.67) 2.7+1.4 kb(0.33)	
71	cCI17-506	D17S545	MspI	3.0 kb(0.33) 2.6 kb(0.67)	17q21
73	cCI17-508	D17S546	MspI	4.6 kb(0.50) 4.0 kb(0.50)	17q25.1-q25.2
80	cCI17-516	D17S550	TaqI	4.1 kb(0.25) 2.4+1.7 kb(0.75)	17q25.1
			PvuII	3.4 kb(0.83) 2.2 kb(0.17)	
88	cCI17-525	D17S866	MspI	2.7 kb(0.42) 2.3 kb(0.58)	
118	cCI17-562	D17S867	TaqI	3.5 kb(0.42) 3.2 kb(0.58)	
			PvuII	7.1 kb(0.92) 6.6 kb(0.08)	
137	cCI17-584	D17S868	MspI	3.8 kb(0.25) 3.6 kb(0.75)	
166	cCI17-615	D17S869	PstI	5.2 kb(0.42) 4.7 kb(0.58)	
243	cCI17-701	D17S870	TaqI 1.7-2.5 kb 6 alleles VNTR,67% heterozygosity also polymorphic with MspI,PstI,PvuII,RsaI		17q21.3
244	cCI17-702	D17S871	MspI	4.1 kb(0.83) 3.4 kb(0.17)	17q25.2-q25.3
			RsaI	5.2 kb(0.83) 4.1 kb(0.17)	
			BglII	6.6 kb(0.83) 5.6 kb(0.17)	
			PvuII	2.9 kb(0.83) 2.2 kb(0.17)	

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Table 5

No.	Probe name	Locus symbol	Enzyme	Allele size (frequency)	Chromosomal localization
245	cCI17-703	D17S877	TaqI 2.6-3.8 kb 4 alleles VNTR,50% heterozygosity also polymorphic with MspI,RsaI,PstI,PvuII		17p13
247	cCI17-705	D17S554	PstI	4.3 kb(0.50) 2.3+2.0 kb(0.50)	17p11.2
250	cCI17-708	D17S878	PvuII 2.6-9.0 kb 10 alleles VNTR,87% heterozygosity also polymorphic with MspI,TaqI,BglII,PstI,EcoRI		17p13
252	cCI17-710	D17S557	MspI 2.0-2.6 kb 5 alleles VNTR,100% heterozygosity also polymorphic with RsaI,TaqI,PstI,PvuII,EcoRI		17q25.3
254	cCI17-712	D17S558	MspI	3.1 kb(0.58) 2.9 kb(0.42)	17p11.2
			TaqI	6.6 kb(0.67) 4.3+2.3 kb(0.33)	
			PvuII	7.1 kb(0.50) 3.9+3.2 kb(0.50)	
255	cCI17-713	D17S559	MspI 2.2-2.8 kb 3 alleles VNTR,50% heterozygosity also polymorphic with PstI		17p13
256	cCI17-714	D17S560	RsaI	4.5 kb(0.58) 4.3 kb(0.42)	17q25.3
			TaqI	3.8 kb(0.75) 2.8 kb(0.25)	
			BglII	3.8 kb(0.58) 3.5 kb(0.42)	
			PvuII	2.6 kb(0.58) 2.4 kb(0.42) 1.5 kb(0.58) 1.4 kb(0.42)	
257	cCI17-715	D17S872	PstI	3.3 kb(0.17) 3.0 kb(0.83)	17q21.3
			EcoRI	3.6 kb(0.87) 3.3 kb(0.13)	
258	cCI17-716	D17S561	TaqI	2.4 kb(0.87) 1.3+1.1 kb(0.13)	17p13
261	cCI17-721	D17S864	RsaI	2.9 kb(0.25) 1.6 kb(0.75)	17q22-q23
			BglII	4.4 kb(0.83) 3.9 kb(0.17)	
262	cCI17-722	D17S563	MspI	4.1 kb(0.83) 3.4 kb(0.17)	17q25.2-q25.3
			RsaI	5.2 kb(0.83) 4.1 kb(0.17)	
			BglII	6.6 kb(0.83) 5.6 kb(0.17)	
			PvuII	2.9 kb(0.83) 2.2 kb(0.17)	
			EcoRI	13.0 kb(0.75) 12.5 kb(0.25)	
263	cCI17-723	D17S873	MspI	3.0 kb(0.33) 1.7 kb(0.67)	17p13
			RsaI	0.8 kb(0.70) 0.5 kb(0.30)	
			TaqI	3.6 kb(0.33) 1.9 kb(0.67)	
			PstI	5.8 kb(0.50) 5.3 kb(0.50)	
			PvuII	4.6 kb(0.58) 4.2 kb(0.42)	
266	cCI17-727	D17S566	PvuII 2.6-9.0 kb 10 alleles VNTR,87% heterozygosity also polymorphic with MspI,TaqI,BglII,PstI,EcoRI		17p13
268	cCI17-729	D17S568	MspI	4.6 kb(0.58) 2.6 kb(0.42)	17q11.2

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Table 6

No.	Probe name	Locus symbol	Enzyme	Allele size (frequency)	Chromosomal localization
269	cCI17-730	D17S874	MspI 2.2-3.5 kb 4 alleles VNTR,83% heterozygosity also polymorphic with TaqI,BglII,PstI,PvuII		17q21.3
270	cCI17-732	D17S570	RsaI	3.2 kb(0.50) 2.7 kb(0.50)	17p13.2
			BglII	8.5 kb(0.50) 3.2 kb(0.50)	
			PstI	2.5 kb(0.58) 1.7 kb(0.42)	
			PvuII	4.2 kb(0.50) 4.1 kb(0.50)	
271	cCI17-733	D17S875	MspI	3.4 kb(0.75) 2.6 kb(0.25)	17q25.1
272	cCI17-735	D17S572	MspI	4.1 kb(0.83) 3.4 kb(0.17)	17q25.3
			RsaI	5.2 kb(0.83) 4.1 kb(0.17)	
			PvuII	2.9 kb(0.83) 2.2 kb(0.17)	
273	cCI17-736	D17S573	TaqI 1.7-2.5 kb 7 alleles VNTR,100% heterozygosity also polymorphic with MspI,RsaI,PstI,PvuII		17q21.3
275	cCI17-739	D17S575	MspI	3.3 kb(0.33) 2.4 kb(0.67)	17q25.1
278	cCI17-743	D17S876	TaqI	4.3 kb(0.17) 2.8 kb(0.83)	

RFLP markers are characterized in that they can be used to distinguish between two alleles inherited from parents by the difference in polymorphism ("informative") [however, they are indistinguishable when both of them have the same polymorphic pattern ("not informative")]. If such a difference in polymorphic pattern between two alleles ("heterozygosity") exists in normal tissues and the loss of heterozygosity (LOH) is detected in tumor tissues, this implies the allelic deletion in the RFLP marker site on a specific chromosome of tumor tissues. It is generally believed that the inactivation of tumor suppressor genes on both alleles, as caused by the deletion of one allele and the mutation in the other, may lead to malignant transformation. Thus, it is assumed that a tumor suppressor gene is present in a region commonly deleted in many cancers.

Using the detailed chromosome map and RFLP markers thus obtained, the present inventors examined about 300 breast cancers and about 100 ovarian cancers for LOH in chromosome 17. As a result, it was revealed that, in informative cases, a region (of 2.4 cM) lying between cosmid markers cCI17-701 and cCI17-730 located in the neighborhood of 17q21 was deleted with high frequency.

Fig. 2 shows partial deletions on chromosome 17q in ovarian cancers. Solid circles represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two commonly deleted regions are designated by sidelines.

Fig. 3 shows partial deletions on chromosome 17q in breast cancers. Solid circles represent the loss of heterozygosity (LOH) and open circles represent the retention of both alleles. Two commonly deleted regions are designated by sidelines.

One of the commonly deleted region partially overlapped with the region in which the presence of a causative gene was suggested by linkage analyses of families affected with hereditary breast cancer. When 650 cases of sporadic breast cancer were examined for somatic rearrangements by Southern-blot analysis using cosmids located to the overlapping region as probes, it was revealed that a partial region in the DNA of cosmid clone cCI17-904, which had been selected as described above, detected amplification. On closer examination of this alterations, it was found that segments each having about 6-9 kb were connected with each other to form an abnormal repetition consisting of about 4-6 copies. Moreover, a gene encoding a novel protein was isolated by screening cDNA (DNA having a complementary base sequence reverse-transcribed from messenger RNA) libraries by using, as probe, a restriction fragment of this cosmid clone having a sequence which was conserved among other species. When the sequence structure of this gene was determined and the presence or absence of genomic alterations of this gene in breast cancers was examined, a distinct gene mutation was identified. These results have revealed that deficiency or mutation

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in this protein and the allelic deletion or mutation of the DNA encoding it deeply participate in the onset of breast and ovarian cancers.

Fig. 4 shows the above-described process starting with a group of markers and leading to the isolation of the gene, as well as the regions where genomic rearrangements occurred in tumor tissues. Clone names are designated by clone numbers alone.

The present invention is very important in that it can provide methods and materials for solving difficult problems (such as risk diagnosis, early finding, course watching, determination of a treatment plan, and estimation of prognosis) concerning at least a part of breast and ovarian cancers, for example, by examining the presence or absence of deficiency or mutation in the protein of the present invention or the presence or absence of the allelic deletion or mutation of the gene encoding it, and thereby bring about a marked advance in the technology in this field.

Specifically, the present invention provides (1) an MDC protein which comprises the whole or part of the protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4, (2) a DNA which comprises the whole or part of the DNA represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9, (3) a plasmid containing the DNA as set forth in the above (2), a transformant carrying the plasmid, i.e., a transformant transformed with the plasmid, and a process for the production of the MDC protein described above, which comprises the steps of culturing the transformant described above and collecting the resulting expression product, (4) an antibody which can bind to the MDC protein described above as an antigen, and (5) a primer, probe or marker which has a DNA sequence comprising a part of the DNA sequence of the DNA as set forth in the above (2), or a DNA sequence complementary to a part of the DNA sequence of the DNA as set forth in the above (2), and a gene analysis method which comprises the step of hybridizing the primer or probe described above to a DNA to be tested.

The term "MDC protein" in this specification means a protein and a peptide (including a oligopeptide and a polypeptide) involved in the definition of the term, "the MDC protein".

Further scope and applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. The present invention will be specifically described hereinbelow.

Detailed Description of the Invention

(1) Isolation of cDNA clones

Cosmid clones having a DNA derived from human chromosome 17 introduced thereinto can be produced, for example, by extracting chromosomal DNA from a human-mouse hybrid cell line containing a single human chromosome 17 in a mouse genomic background, and incorporating fragments of the chromosomal DNA into a vector such as pWEX15, according to a method reported by Tokino et al. (Tokino et al., Am. J. Hum. Genet., 48, 258-268, 1991). From among them, clones having an insert derived from the human chromosome can be selected by colony hybridization using the whole human DNA as probe.

The map position of each of the cosmid clones can be determined by FISH. Then, they can be used as markers to construct a high resolution physical chromosome map. Moreover, RFLP markers can be selected on the basis of the fragment length pattern in southern blot analysis (Nakamura et al., Am. J. Hum. Genet., 43, 854-859, 1988). If this map and these RFLP markers are utilized to examine DNAs obtained from the tumor tissues of cancer patients for LOH (loss of heterozygosity), the commonly deleted region on the chromosome in the tumor tissues can be localized to a very small region near q21 of chromosome 17.

Southern-blot analysis of the DNAs from tumor tissues by using a cosmid clone, whose hybridizable portion is present in this localized region, as probe makes it possible to select clones having a DNA sequence associated with genomic alterations in the tumor tissues. Moreover, Southern-blot analysis of the chromosomal DNAs of various mammals by using restriction fragments of the cosmid clone as probes makes it possible to select a fragment containing a DNA sequence conserved among other species and involved in fundamental cellular functions. DNA sequences encoding important proteins are often conserved among other species. In fact, many of the hitherto isolated genes for hereditary diseases are conserved

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among other species (Call, K.M. et al., Cell, 60, 509-520, 1990).

If the DNA fragment thus obtained is used as probe, the cDNA of the gene present in a localized region near q21 of human chromosome 17 can be cloned. The base sequence of this cDNA can be determined by a conventional manner (Maniatis, J. et al., Molecular Cloning 2nd. ed., Cold Spring Harbor Laboratory Press, N.Y. 1989).

In order to confirm that the DNA clones thus obtained are clones of the desired causative gene, their sequences may be used to examine the presence or absence of genomic alterations in cancer patients and the incidence of genomic alterations according to the SSCP method (Orita, M. et al., Genomics, 5, 874-879, 1984; Orita, M. et al., Cell, 60, 509-520, 1990), the RNase protection method (Winter, E., Perucho, M. et al., Proc. Natl. Acad. Sci. USA, 82, 7575-7579, 1985; Myers, R.M. et al., Science, 230, 1242-1246, 1985) and other methods.

(2) Confirmation of the whole structure of the gene

It has been confirmed that the DNA sequences of two cDNAs obtained by the above-described procedure are novel and are those of the DNAs represented by SEQ ID NO:6 and SEQ ID NO:7. The corresponding amino acid sequences have also been identified as those of the proteins represented by SEQ ID NO:2 and SEQ ID NO:3. Moreover, 5'-RACE and RT-PCR have revealed the DNA sequence of the DNA represented by SEQ ID NO:8, and the amino acid sequence of the protein represented by SEQ ID NO:4 has been deduced as one corresponding to the DNA sequence. Furthermore, with regard to genomic DNA, the structure of the DNA represented by SEQ ID NO:9 including introns and exons has been revealed by analyzing the base sequence of the original cosmid clone cCI17-904 and comparing it with the base sequence of the isolated cDNA clone to determine the intron-exon junctions.

By the present inventors, proteins comprising the whole or part of the amino acid sequence of the protein represented by SEQ ID NO:1, which is an amino acid sequence common to all of the above-described proteins, are named MDC proteins and will hereinafter be referred to as MDC proteins.

The term "a part of the protein" means, for example, a polypeptide having or comprising an amino acid sequence consisting of a continuous, at least three amino acids which is described in SEQ ID NO:1. The amino acid sequence consists of preferably at least three to five amino acids, still more preferably at least eight or at least eight to ten amino acids, and most preferably at least eleven to twenty amino acids. It is to be understood that polypeptides each having or comprising an amino acid sequence consisting of a continuous, more than 20 amino acids which is described in SEQ ID NO:1 can also be used.

As used herein, the term "substantially equivalent" means that, in proteins comprising the whole or part of the amino acid sequence of the protein represented by, for example, SEQ ID NO:1, their amino acid sequences are attended with the replacement, deletion and/or insertion of one or more amino acids, but they can produce an equal effect in research and diagnosis using the proteins comprising the whole or part of the amino acid sequence of the protein represented by, for example, SEQ ID NO:1. Such equivalents also fall within the scope of the present invention and also called as MDC proteins.

The DNA sequence common to all DNAs encoding MDC proteins is one of the DNA represented by SEQ ID NO:5.

A DNA in accordance with the present invention can be utilized in gene analysis and diagnosis. That is, a primer or probe comprising a part of the DNA sequence of the DNA according to the present invention, or comprising a DNA sequence complementary to a part of the DNA sequence of the DNA according to the present invention is used in gene analysis and diagnosis.

Part of the DNA sequence consists of at least six bases, preferably at least 8 bases, still more preferably 10-12 bases and particularly preferably about 15-25 bases. That is, the oligonucleotide used as primer or probe comprises at least six bases derived from the DNA sequence of the DNA according to the present invention or derived from the DNA sequence complementary to the DNA sequence of the DNA according to the present invention, and, if necessary, other base(s).

In connection with the DNAs of the present invention, the term "substantially equivalent" has the same meaning as described above for the proteins, except that their base sequences are attended with the replacement, deletion and/or insertion of one or more bases.

The introduction of replacement, deletion and insertion mutations into a particular base sequence can be accomplished according to any of conventional methods including those described in F.M. Ausubel et al., "Current Protocols in Molecular Biology", 1987, Chapter 8.

The MDC protein encoded by the DNA according to the present invention, i.e., the MDC protein according to the present invention, can be utilized by using it as an epitope to prepare an antibody. This antibody can be used in experimental and diagnostic reagents. The term "epitope" means an antigenic

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determinant of a polypeptide and is generally composed of at least 5 amino acids. It is well known that a polypeptide composed of 6 amino acids binds with an antibody, as disclosed in, for example, Published Japanese Translation of International Patent Application No. 60-500684.

(3) Recombinant expression vectors and transformants generated therewith

A transformant can be obtained by incorporating a DNA encoding human MDC protein, which has been obtained by the above-described procedure, or a fragment thereof into a suitable vector and introducing this vector into suitable host cells. By culturing this transformant with a conventional manner, large amounts of human MDC protein can be obtained from the culture. More specifically, a recombinant expression vector can be produced by linking a DNA encoding a human MDC protein or a fragment thereof on the downstream side of the promoter of a vector suited for its expression according to a well-known method using restriction enzymes and DNA ligase. Usable vectors include, for example, plasmids pRB322 and pUC18 derived from Escherichia coli, plasmid pUB110 derived from Bacillus subtilis, plasmid pRB15 derived from yeast, phage vectors λgt10 and λgt11, and vector SV40 derived from an animal virus. However, no particular limitation is placed on the type of vector used, so long as it can be replicated and amplified in the host. Similarly, no particular limitation is placed on the promoter and terminator, so long as they are compatible with the host used for the expression of the DNA base sequence encoding the human MDC protein. They may be used in any suitable combination depending on the host. The DNA used can be any of DNAs encoding human MDC protein. It is not limited to the base sequences represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 and SEQ ID NO:9, but can be any of DNAs in which a part of the base sequence has undergone replacement, deletion, insertion or a combination thereof, whether intentionally or not. In addition, chemically synthesized DNAs can also be used.

A transformant is generated by introducing the recombinant expression vector thus obtained into a host according to the competent cell method (J. Mol. Biol., 53, 154, 1970), the protoplast method (Proc. Natl. Acad. Sci. USA, 75, 1929, 1978), the calcium phosphate method (Science, 221, 551, 1983), the in vitro packaging method (Proc. Natl. Acad. Sci. USA, 72, 581, 1975) or the virus vector method (Cell, 37, 1053, 1984). The host used can be Escherichia coli, Bacillus subtilis, yeast or animal cells, and the resulting transformant is grown in a suitable medium depending on the host. Usually, the transformant is grown at a temperature of 20 to 45°C and a pH of 5 to 8, optionally with aeration and stirring. Separation and purification of the MDC protein from the culture may be carried out using a suitable combination of well-known separation and purification techniques. These well-known techniques include salting-out, solvent precipitation, dialysis, gel filtration, electrophoresis, ion exchange chromatography, affinity chromatography, reverse-phase high-performance liquid chromatography and the like.

(4) Preparation of antibodies

Antibodies can be prepared in the usual manner by using an antigen of which epitope part comprises an MDC protein. For example, a polyclonal antibody can be prepared by fully immunizing an animal such as mouse, guinea pig and rabbit through a plurality of subcutaneous, intramuscular, intraperitoneal or intravenous injections of the antigen described above, collecting blood from this animal, and separating serum therefrom. Commercially available adjuvants may also be used.

A monoclonal antibody can be prepared, for example, by immunizing a mouse with the antigen described above, fusing its spleen cells with commercially available mouse myeloma cells to produce a hybridoma, and collecting an antibody from the culture supernatant of the hybridoma or the ascites of a mouse inoculated with the hybridoma.

The MDC protein which is used as antigen or is used to prepare an antigen need not necessarily have the whole amino acid structure described in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4, but may have a partial structure of the amino acid sequence described in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4. Alternatively, the MDC protein may be a variant or derivative of the MDC protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4. The antigen may be an MDC protein as such, or a fusion peptide consisting of an MDC protein (incluing peptide) and another peptide. Preparation of the fusion peptide may be carried out according to either biological techniques or chemical synthesis techniques.

These antibodies enable identification and determination of the MDC protein present in human biological specimens and can hence be used as reagents for the diagnosis of cancer, and the like.

The immunological determination of the MDC protein can be made according to any conventional technique. For example, any of the fluorescent antibody technique, the passive agglutination technique and

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the enzyme antibody technique may be employed.

(5) Gene analysis of human tumor tissues

The biological specimens which can be used for gene analysis include human normal tissues and various types of human tumor tissues, as well as human blood, human body fluids, human secretions and the like. The extraction and preparation of DNA can be carried out, for example, according to the method of Sato et al. (Sato, T. et al., Cancer Res., 50, 7184, 1990).

The presence or absence of mutations of the gene can be analyzed by using, as probes, a restriction fragment of the DNA encoding human MDC protein as provided by the present invention, or by selecting a properly located base sequence from the DNA, synthesizing an oligonucleotide having the selected base sequence and using the oligonucleotide as primer.

These analyses can also detect other alterations, such as insertion and deletion, of the gene in samples.

The base sequences selected for this purpose can be exon portions, intron portions, or junction portions therebetween. It is a matter of course that artificially modified base sequences may be used. When an artificially modified base sequence is used to prepare primer, the corresponding gene mutation can be detected by the gene analysis.

Analyses can be carried out, for example, by amplifying a partial sequence by PCR using two selected sequences as primers and analyzing the base sequence of the amplification product directly, or by incorporating the amplification product into a plasmid in the same manner as that described above, transforming host cells with this plasmid, culturing the transformed cells, and analyzing the base sequence of the clone thus obtained. Alternatively, the presence or absence of particular mutations of the gene in samples can be directly detected by the use of the ligase chain reaction method (Wu et al., Genomics, 4, 560-569, 1989) and, moreover, the mutant sequence specific PCR method (Ruano and Kidd, Nucleic Acid Research, 17, 8392, 1989; C.R. Newton et al., Nucleic Acid Research, 17, 2503-2517, 1989).

Similarly, using probes containing DNA sequences selected or RNA sequences derived therefrom, point mutations can be detected by the SSCP method or the RNase protection method. Moreover, use of these probes also makes it possible to detect mutations of the gene in samples by Southern hybridization and abnormalities in the expression level of the gene in samples by northern hybridization.

Escherichia coli DH5/pBR1 and Escherichia coli XL1-Blue MRF'Kan/pCR-5P2, each carrying a plasmid containing the DNA encoding this MDC protein, and Escherichia coli 490A/cCI 17-904, carrying a cosmid containing the genomic DNA, were deposited with the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry on April 28, 1993, February 8, 1994 and April 28, 1993 under accession numbers FERM BP-4286, FERM BP-4555 and FERM BP-4287, respectively.

The MDC proteins and DNAs encoding the MDC proteins according to the present invention are expected to be useful as reagents for cancer research, testing and diagnostic reagents, and therapeutic agents.

Examples

The present invention will now be described in more detail with reference to the following Examples which should not be considered to limit the scope of the present invention.

Example 1 Isolation of cosmid clones specific for human chromosome 17 and construction of a chromosome map

A human-mouse hybrid cell line (GM10331) containing a single human chromosome 17 in a mouse genomic background was selected from among hybrid cells produced by fusing human normal cells with cells of an established mouse cell line and cosmid clones specific for human chromosome 17 were isolated according to the method of Tokino et al. (Tokino et al., Am. J. Hum. Genet., 48, 258-268, 1991). The chromosomal DNA of this hybrid cell line was properly digested with restriction enzyme Sau 3AI and the ends of the fragments thus obtained were treated by partial filling-in with dATP and dGTP. Fragments having a size of 35-42 kb were separated therefrom and inserted in cosmid vector pWEX15 which had previously been digested with restriction enzyme Xho I and similarly treated at its ends by partial filling-in with dCTP and dTTP. From among the resulting cosmid clones, clones containing human DNA fragments were selected by colony hybridization using ^{32}P-labeled human chromosomal DNA as probe. Thus, 342

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cosmid clones specific for human chromosome 17 were isolated.

With regard to each of these cosmid clones specific for human chromosome 17, the location to which its cosmid DNA hybridize on the chromosome was determined by FISH (Inazawa et al., Genomics, 10, 1075-1078, 1991). Thus, a physical chromosome map for chromosome 17 was constructed (see Tables 1-3 and Fig. 1).

Using DNAs obtained from 6 unrelated individuals, the cosmid clones (cosmid markers), the locations on the chromosome to which their cosmid DNA hybridize had been determined, were examined by a known method (Nakamura et al., Am. J. Hum. Genet., 43, 854-859, 1988) in order to see whether RFLP could be detected or not. The restriction enzyme used was Msp I, Taq I, Bgl II, Pst I, Pvu II, Rsa I or Eco RI. As a result, RFLP was detected in 43 clones (see Tables 4-6). That is, these 43 clones were usable as RFLP markers.

Example 2 Detection of commonly deleted regions of the human chromosome 17q in ovarian and breast cancers

Tumor tissues were obtained from 94 patients with ovarian cancer and 246 patients with breast cancer who underwent surgery. Corresponding normal tissues or peripheral blood samples were also obtained from the respective patients. DNAs were extracted from these tissues or samples according to a known method (Sato et al., Cancer Res., 50, 7184-7189, 1990). Each DNA was digested with suitable restriction enzymes, and the fragments thus obtained were subjected to 1.0% agarose gel electrophoresis and then Southern transferred to a nylon membrane with 0.1N NaOH/0.1M NaCl (Sato et al., Cancer Res., 50, 7184-7189, 1990).

The membranes thus obtained were examined for LOH (loss of heterozygosity) by Southern hybridization (Sato et al., Cancer Res., 50, 7184-7189, 1990) using, as probes, the RFLP markers obtained by the procedure of Example 1 (see Table 7).

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Table 7

Probe	Chromosomal location	Enzyme	Ovarian Cancer: No.of patients tested: serous	mucinous	clear cell	others	Ovarian Cancer: allelic losses/infomative cases(%): serous	mucinous	clear cell	others	Breast Cancer: No.of patients tested	Breast Cancer: allelic losses/ infomative cases (%)
C117-316	q12-21.1	MspI	32	15	12	22	6/13(46.2)	0/1(0.0)	0/3(0.0)	1/9(11.1)	85	11/37(29.7)
C117-592	q21.3	EcoRI	14	13	9	15	2/3(66.7)	0/1(0.0)	0/1(0.0)	2/4(50.0)	62	8/18(44.4)
C117-701	q21.3	TaqI	24	14	13	19	9/15(60.0)	2/12(16.7)	0/7(0.0)	5/12(41.7)	232	48/138(34.8)
C117-730	q21.3	TaqI	29	15	13	19	6/12(50.0)	0/4(0.0)	0/4(0.0)	2/4(50.0)	237	36/96(37.5)
C117-507	q21.3	MspI	22	14	11	20	6/7(85.7)	1/3(33.3)	1/3(33.3)	2/5(40.0)	74	7/25(28.0)
C117-533	q21.3	TaqI	22	13	11	16	6/11(54.5)	3/9(33.3)	1/7(14.3)	4/9(44.4)	230	25/93(26.9)
C117-7	q22	PvuII	21	8	9	15	4/5(80.0)	0/1(0.0)	0/3(0.0)	1/3(33.3)	86	14/41(34.1)
C117-489	q23	MspI	26	13	11	21	5/5(100.0)	0/2(0.0)	0/3(0.0)	3/8(37.5)	75	10/31(32.3)
CMM86	q23	TaqI	28	13	10	17	6/17(35.3)	1/8(12.5)	0/6(0.0)	2/10(20.0)	79	12/49(24.5)
C117-516	q25.1	TaqI	29	14	14	21	6/17(35.3)	1/10(10.0)	0/7(0.0)	6/11(54.5)	84	9/31(29.0)
C117-710	q25.3	TaqI	18	13	10	12	4/8(50.0)	3/8(37.5)	0/6(0.0)	3/7(42.9)	80	13/45(28.9)

A total of 84 among 94 ovarian tumors were informative for at least one locus, and 33 (39.3%) of them showed LOH for at least one locus on chromosome 17q. Among 246 breast tumors examined, 214 were informative for at least one locus, and 88 (41.4%) showed LOH for at least one locus on chromosome 17q.

From the above results, the instances which were informative for two or more loci and exhibited both loss of heterozygosity at a locus and retaining of heterozygosity at other locus on chromosome 17q were

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summarized.

As a result, two commonly deleted regions were found in 8 ovarian cancers (see Fig. 2). One of them was a region lying between markers CI17-316 (17q12-21.1) and CI17-507 (17q21.3), and the other was a region distal to the marker CI17-516 (17q25.1).

Similarly, two commonly deleted regions were found in 35 breast cancers (see Fig. 3). One of them was a region lying between markers CI17-701 (17q21.3) and CI17-730 (17q21.3), which was also found in the ovarian cancers but was more narrowly localized. The other was a region lying on the terminal side of marker CI17-516 (17q25.1), which was also the region where a deletion was observed in the ovarian cancers.

Of the two commonly deleted regions defined by the above-described deletion mapping, the region flanked by markers CI17-701 and CI17-730 was found to lie close to the 17q21 region showing an intimate correlation with the onset of cancer on the basis of the results of linkage mapping studies on hereditary breast cancer and ovarian cancer (Hall et al., Am. J. Hum. Genet., 50, 1235-1242, 1992). The length of this region (i.e., the genetic distance between the two markers) was estimated to be 2.4 cM by linkage analysis (Lathrop et al., Am. J. Hum. Genet., 37, 482-498, 1985; Donis-Keller et al., Cell, 51, 319-337, 1987).

Example 3 Isolation of cosmid clones contained in the minimal localized region

Since it has been shown that the region localized on the basis of the results of linkage mapping is a region lying between markers THRA1 and Mfd188 on 17q21 (Hall et al., Am. J. Hum. Genet., 52, 1235-1242, 1992; Bowcock, A.M. et al., Am. J. Hum. Genet., 52, 718-22, 1993), an attempt was made to determine the relative order of these markers and markers CI17-701 and CI17-730 and thereby combine the mapping information obtained by two different strategies. The relative order of the markers was determined by a two-color FISH method newly developed by the present inventors. This method is a modification of FISH in which a highly extended chromosome preparation obtained by synchronization of the cells is used to enhance the degree of fineness and, moreover, probes labeled with fluorescent materials having different colors are used. This method makes it possible to determine the relative order of markers very close to each other.

As a result, it was found that marker Mfd188 lies between markers CI17-701 and CI17-730 and marker THRA1 lies on the centromeric side of CI17-701 (see Fig. 4, a). That is, the region associated with hereditary breast cancer as localized by linkage mapping and the commonly deleted region in sporadic breast cancers as localized by deletion mapping overlapped each other and the overlapping minimal region was flanked by markers CI17-701 and Mfd188 (see Fig. 4, a). When a physical map of this region was constructed by pulsed-field gel electrophoresis, the length of the overlapping region was greatly narrowed down to about 500 kb.

Furthermore, of the cosmid clones obtained by the procedure of Example 1, 37 clones localized to 17q21.3 and three known markers, THRA1, Mfd188 and PPY, were selected and used for fine mapping of this chromosomal region by two-color FISH. As a result, 15 cosmid clones were located in a region flanked by markers CI17-701 and CI17-730. Of these, two cosmid clones, CI17-527 and CI17-904, were found to lie in the above-described overlapping region (see Fig. 4, a and b).

Example 4 Detection of genomic alterations in breast cancers

Of the overlapping region of about 500 kb, about 150 kb has already been covered by four cosmid clones CI17-701, CI17-527, CI17-904 and Mfd188. Accordingly, an attempt was first made to screen restriction (Sac I, Pvu II or Pst I) fragments of the DNAs from the tumor tissues of 650 sporadic breast cancers by Southern-blot analysis using the DNAs of these cosmid clones or fragments thereof as probes and thereby detect gross structural genomic alterations (so-called genomic rearrangements), such as deletion, duplication, amplification and translocation, having occurred in the tumor cells. As a result, when the DNA of CI17-904 or its 9.5 kb Hind III fragment (see Fig. 4, c) was used as probe, genomic rearrangements were detected in the tumor tissues of two breast cancers (see Fig. 5, a and b). These genomic rearrangements occurred only in the tumor tissues, exhibiting extra bands of different size which were not observed in normal tissues. In addition, the intensities of some bands were increased. That is, a gene amplification occurred in a definite DNA region corresponding to (i.e., hybridizable) this probe. In one case among the above-mentioned two breast cancers, no gene amplification was detected when Southern-blot analysis of the Sac I fragments of DNA from the breast cancer tissue was carried out by using the E-H5.2 or Hind6.1 fragment adjacent to the 9.5 kb Hind III fragment (see Fig. 4, c) as probe (see Fig. 6, Case 1). This indicates that the gene amplification in this case occurred within the region corresponding to the 9.5

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kb Hind III fragment and was a 4- to 5-fold amplification.

For purpose of closer examination, Southern-blot analyses of the Sac I fragments of DNA from the breast cancer tissue were carried out using each of six Sac I fragments derived from the 9.5 kb Hind III fragment, A, B, C, D, E and F (see Fig. 4, c), as probe. As a result, amplified bands of abnormal size were observed at 2.5 kb with probes A and B, at 3.0 kb with probes B, C and D, at 2.5 kb with probes E and F, and at 0.9 kb with probe F (see Fig. 7).

In the other case, gene amplification was detected when Southern-blot analysis of the Sac I fragments of DNA from the breast cancer tissue was carried out by using the E-H5.2 fragment as probe (see Fig. 6, Case 2). However, no gene amplification was detected when the Hind6.1 fragment was used as probe (see Fig. 6, Case 2). In this case, when the E-H5.2 fragment was used as probe, only an amplification was observed without being attended with any band of abnormal size. This indicates that the gene amplification in this case occurred in a segment extending from within the region corresponding to the 9.5 kb HindIII fragment to the outer (telomeric) side of the region corresponding to the E-H5.2 fragment.

Example 5 Isolation of cDNA and determination of its structure

In order to isolate an expressed gene in or near the region where genomic rearrangements were detected in the two breast cancers, DNA fragments containing DNA sequences involved in fundamental cellular functions and conserved among other species were selected from DNA fragments of cosmid clone CI17-904. Specifically, each of the DNA fragments of cosmid clone CI17-904 was used as probe in Southern blot hybridization analyses of DNA fragments from cow, pig, mouse, rat and chicken. As a result, the 3.5 kb Hind III-Ksp I fragment (see Fig. 4, c) of cosmid clone CI17-904 hybridized to DNAs from cow, pig, mouse and rat and showed strong conservation.

Using this 3.5 kb Hind III-Ksp I fragment as probe, human cDNA libraries derived from five different organs (i.e., mammary gland, breast cancer cell line, fetal brain, cerebrum and cerebellum) were screened. Thus, the longest cDNA was cloned from the cerebellar cDNA library. This cDNA hybridized to the 3.5 kb Hind III-Ksp I fragment of cosmid clone CI17-904 and a plurality of adjoining restriction fragments, and extended over a region of more than 20 kb on the chromosome.

Analysis of the base sequence of this cDNA revealed that it consisted of 2923 base pairs (bp) and was a novel DNA base sequence containing a 5'-untranslated region of 27 bp, a coding region of 1575 bp, a 3'-untranslated region of 1306 bp, and a poly(A) tail of 15 bp (see SEQ ID NO:6). The open reading frame contained in this cDNA sequence encoded a novel protein (MDC protein; see SEQ ID NO:2). An in-frame termination codon was present immediately upstream of the first ATG of the open reading frame. A polyadenylation signal, AATAAA, was observed about 20 bp upstream from the polyadenylation site.

Example 6 Determination of the structure of genomic DNA

In order to clarify the structure of the genomic DNA corresponding to the cDNA obtained in Example 5, cosmid clone CI17-904 was examined to determine the base sequences of portions containing the base sequence of this cDNA and portions surrounding them. Then, the sequences of both were compared to determine the exon-intron junctions. As a result, the sequence structure of a novel DNA containing 25 exons corresponding to the cDNA obtained in Example 5 was clarified (see SEQ ID NO:9). Thus, it was shown that these 25 exons are of relatively small size and present over an about 20 kb region of the chromosome.

Example 7 Detection of alterations in the exon structure of the gene in breast cancers

From the structure of the DNA containing exons/introns as clarified in Example 6, it has become apparent that exons 2, 3 and 4 are present in the sequence region of the probe (the 9.5 kb Hind III fragment of cosmid clone CI17-904) with which alterations were detected in the tumor tissues of two breast cancers as described in Example 4. More specifically, exon 2 is present in the sequence region of probe E, and exons 3 and 4 are present in the sequence region of probe F (see Fig. 4, c). Accordingly, it is believed that the gene rearrangements involving the 9.5 kb Hind III fragment region as described in Example 4 disrupt the normal exon structure in the region containing the three exons of the gene. In order to confirm this, the chromosomal DNAs from the tumor tissues of the above-described two breast cancers were examined by Southern-blot analysis using probes having DNA sequences corresponding to exons 2, 3 and 4. Thus, amplified bands of abnormal size were observed similarly to the previously described results obtained with probe E or F (see Fig. 7).

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Example 8 Tissue specificity of gene expression

mRNAs derived from various human tissues (brain, heart, kidney, liver, lung, pancreas, placenta, skeletal muscle, colon, peripheral blood lymphocyte, ovary, small intestine, spleen, testis and thymus) were examined by northern-blot analysis using the cDNA obtained in Example 5 as probe. As a result, the strongest expression was observed in the brain, and a weak expression in the heart, ovary and testis.

Moreover, amplification by RT-PCR (reverse-transcriptase PCR) was performed to detect a weaker expression. Specifically, using random hexamers as primers, single-stranded cDNAs were synthesized from mRNAs derived from various human tissues under the action of reverse transcriptase. Then, PCR amplification from these templates was performed using primers BCO9 and BCO12 having sequences derived from the sequences of exons 21 and 23, respectively, which had been revealed in Example 6. As a result, a PCR product having the expected size was observed mainly in tissues of the central nervous system (cerebrum, cerebellum and fetal brain) and in endocrine or reproductive organs (testis, ovary, mammary gland, adrenal gland, thymus and pancreas).

The sequences of the primers used are as follows:

BCO9 5'-GCACCTGCCCCGGCAGT-3' (SEQ ID NO:10) (coding strand, corresponding to base numbers 1764-1780 of SEQ ID NO:6)

BCO12 5'-CCAGGACAGCCCCAGCGATG-3' (SEQ ID NO:11) (antisense strand, corresponding to base numbers 1976-1957 of SEQ ID NO:6)

Example 9 Direct sequencing of mRNA by RT-PCR

mRNAs derived from human fetal brain and human testis were amplified by RT-PCR using primer GMA701 having a sequence derived from the sequence on exon 19 and primer GMB704 having a sequence derived from the sequence on exon 21. Then, the base sequences of the amplified DNAs were directly determined using primer GMA702 or GMB703. As a result, a sequence, wherein 10 bases (base numbers 1512-1521) were deleted from the cerebellar cDNA sequence of SEQ ID NO:6 obtained in Example 5, was found, which revealed the expression of mRNA corresponding to the DNA sequence of SEQ ID NO:7. Both of the fetal brain and testis mRNAs gave the identical result. The open reading frame contained in the cDNA sequence of SEQ ID NO:7 encodes an MDC protein (see SEQ ID NO:3) composed of 670 amino acids.

This seems to be caused by the alternative RNA splicing at the initiation of exon 20 which starts with base number 6083 instead of base number 6078 on the genomic DNA of SEQ ID NO:9. Such a variation of splicing is also known from. for example. a report by Oda et al. [Biochem. Biophys. Res. Commun., 193, 897-904 (1993)]. As a result, the amino acid sequences encoded by the cDNA of SEQ ID NO:6 and the cDNA of SEQ ID NO:7 differ from each other at and after that site (see SEQ ID NO:2 and SEQ ID NO:3). Specifically, the cDNA of SEQ ID NO:6 produces a termination codon within exon 20, whereas the reading frame is shifted in the cDNA of SEQ ID NO:7 so as to cause the open reading frame to continue to a more downstream position.

The sequences of the primers used in PCR and DNA sequencing are as follows:

GMA701 5'-GGCTGCTGATCGCTTCTGCTAC-3' (SEQ ID NO:12) (coding strand, corresponding to base numbers 1413-1434 in SEQ ID NO:6)

GMA702 5'-GAGAAGCTGAATGTGGAGGG-3' (SEQ ID NO:13) (coding strand, corresponding to base numbers 1435-1456 in SEQ ID NO:6)

GMB703 5'-GTCAGAGCCGTCCGCCAGC-3' (SEQ ID NO:14) (antisense strand, corresponding to base numbers 1675-1657 in SEQ ID NO:6)

GMB704 5'-GCCATCCTCCACATAGCTCAGG-3' (SEQ ID NO:15) (antisense strand, corresponding to base numbers 1696-1655 in SEQ ID NO:6)

Example 10 Amplification of the 5'-terminal sequence by RACE

In order to obtain the full-length cDNA represented by SEQ ID NO:7, PCR amplification of the 5'-cDNA terminus (5'-RACE; Frohman, et al., Proc. Natl. Acad. Sci. USA, 85, 8998-9002, 1988; Belyavski, et al., Nucleic Acid Res., 17, 2919-2932, 1988) was performed. Using specific oligomer SGN012 as primer, together with a commercially available synthesis kit, a single-stranded cDNA was synthesized from 2 μg of poly A(+) RNA derived from human brain (manufactured by Clontech). Then, 5'-RACE was performed using a commercially available kit based on the method of Edwards et al. for linking an anchor oligomer to an end of a single-stranded cDNA (Nucleic Acid Res., 19, 5227-5232, 1991). As a result of PCR using the

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anchor oligomer of the kit and another specific oligomer SGN011 as primers, an amplification product of about 580 bp was detected by electrophoresis.

This amplification product was extracted from the electrophoretic gel, purified, inserted in the Srf I cleavage site of plasmid vector pCR-Script (manufactured by Stratagene), and cloned. Plasmid DNA was purified from each clone and its base sequence was determined. One of the clones, pCR-5P2, had a cDNA insert of 501 bp beginning with ATG, next to the sequence of the anchor oligomer. The base sequence of the insert extending from base number 315 onward coincided exactly with the base sequence of SEQ ID NO:7 extending from base number 45 (the initiation site of exon 2) onward, excepting one base which will be mentioned below. Furthermore, as far as the reading frame is concerned, that of pCR-5P2 beginning with the first ATG corresponded with the polypeptide encoded by the cDNA of SEQ ID NO:7. The N-terminal region of the polypeptide sequence thus obtained encoded a signal peptide comprising a series of hydrophobic amino acids.

RT-PCR was performed in order to confirm that the above 5'-terminal sequence obtained by 5'-RACE was truly linked, on mRNA, to the sequence of SEQ ID NO:7 extending from base number 45 onward. Using random hexamers as primers, single-stranded cDNAs were synthesized from poly A(+) RNAs derived from human brain, fetal brain, ovary and testis (manufactured by Clontech). Then, the cDNA template were amplified by PCR using an oligomer (SGN013) having the first 20-base sequence of pCR-5P2 as sense primer and SGN011 or SGN012 as antisense primer. As a result, the expected amplification product (about 500 bp for SGN013/SGN011 and about 750 bp for SGN013/SGN012) was detected by electrophoresis with every tissue RNA used.

Thus, it was confirmed that the 5'-terminal sequence of pCR-5P2 obtained by 5'-RACE was linked, on mRNA, to the sequence of SEQ ID NO:7 extending from base number 45 onward, resulting in the construction of a cDNA represented by SEQ ID NO:8. The open reading frame of the cDNA of SEQ ID NO:8 encodes an MDC protein composed of 769 amino acids (see SEQ ID NO:4).

The sequences of the specific oligomers used are as follows:

SGN011 5'-GATGTAAGTCAAGTTCCCATCAGAGA-3' (SEQ ID NO:16) (antisense strand, corresponding to base numbers 231-206 in SEQ ID NO:7)

SGN012 5'-AACAGCTGGTGGTCGTTGATCACAA-3' (SEQ ID NO:17) (antisense strand, corresponding to base numbers 485-461 in SEQ ID NO:7)

SGN013 5'-ATGAGGCTGCTGCGGCGCTG-3' (SEQ ID NO:18) (coding strand, corresponding to base numbers 1-20 in SEQ ID NO:8)

The above-mentioned one base in the SEQ ID NO:8 after the initiation site of exon 2, differing from one in the SEQ ID NO:6 or SEQ ID NO:7, is the forth base from the initiation site of exon 2, i.e., the C at the base number 318 in the SEQ ID NO:8. The corresponding base in the SEQ ID NO:6 or the SEQ ID NO:7 is the A at the base number 48. The base C at the base number 318 in the SEQ ID NO:8 codes His at the amino acid number 106 in the SEQ ID NO:4. The base A at the base number 48 in the SEQ ID NO:6 or the SEQ ID NO:7 codes Gln at the amino acid number 7 in the SEQ ID NO:2 or the SEQ ID NO:3. This fact reflects polymorphism.

An amino acid sequence common to these three variant MDC proteins (SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4) is a sequence composed of 488 amino acids (see SEQ ID NO:1), and a DNA sequence encoding this portion is also a common sequence (see SEQ ID NO:5).

Example 11 Homology with known proteins

The amino acid sequences of MDC proteins showed homology with a family of snake venom hemorrhagic proteins including HR1B (Takeya et al., J. Biol. Chem., 265, 16068-16073, 1990), prorhodostomin (Au et al., Biochem. Biophys. Res. Commun., 181, 585-593, 1991) and protrigramin (Neeper et al., Nucleic Acid Res., 18, 4255, 1990).

They also showed homology with the guinea pig sperm surface protein PH30 (Blobel et al., Nature, 356, 248-252, 1992) and the rat or monkey epididymis protein EAPI (Perry et al., Biochem. J., 286, 671-675, 1992).

The homology of these proteins with the MDC proteins represented by SEQ ID NO:2 (524 amino acids) and SEQ ID NO:4 (769 amino acids) is indicated by the following "percent identity/number of amino acids in the tested region". The values for SEQ ID NO:2 are given on the left side and those for SEQ ID NO:4 on the right side.

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HR1B	32.5/335	32.2/379
prorhodostomin	29.0/420	29.0/420
protrigramin	27.7/430	28.1/438
PH30b	38.1/147	30.8/302
EAP1 (rat)	36.0/364	33.1/475
EAP1 (monkey)	30.4/503	29.9/599

Example 12 Generation of transformants

A DNA fragment encoding a part of the MDC protein represented by SEQ ID NO:2 was amplified from the DNA (SEQ ID NO:6) encoding the MDC protein (SEQ ID NO:2) by PCR using primers SGN006 and SGN008. The sequences of the primers used are as follows.

SGN006 5'-CACAGATCTGGGGGCATATGCTCCCTG-3' (SEQ ID NO:19) (coding strand, corresponding to base numbers 766-783 in SEQ ID NO:6)

SGN008 5,-AACAAGCTTCTACTGATGTCTCCCACC-3' (SEQ ID NO:20) (antisense strand, corresponding to base numbers 1602-1585 in SEQ ID NO:6; the underline designating a termination codon.)

For purposes of vector construction, the 5'-terminal of these primers are provided with Bgl II and Hind III cleavage site sequences, respectively.

The PCR amplification product was separated by agarose gel electrophoresis and cleaved with Bgl II and Hind III. The resulting DNA fragments encoding a part of the MDC protein was combined with vector pMAL-c2 (manufactured by New England Biolabs) which had previously been cleaved with Bam HI and Hind III to construct plasmid pMAL-MDC(C1).

Similarly, the same DNA fragment was combined with vector pQE-13 (manufactured by Diagen) which had previously been cleaved with Bam HI and Hind III to construct plasmid pH6-MDC(C1).

Furthermore, a DNA sequence downstream from the Bam HI cleavage site (base number 1483 in SEQ ID NO:6) was removed from the MDC protein encoding region of pMAL-MDC(C1) by cleaving pMAL-MDC-(C1) with Bam HI and Hind III, and recombining it after the formation of blunt ends. This resulted in the construction of plasmid pMAL-MDC(dC1), which mediates expression of a polypeptide with amino acid sequence common to two variant MDC proteins (SEQ ID NO:2 and SEQ ID NO:3).

Since the fragment incorporated into vector pMAL-c2 is expressed as a fusion protein having a maltose-binding protein (MBP) on the N-terminal side, this fusion protein was purified by affinity chromatography using an amylose column. On the other hand, since the fragment incorporated into vector pQE-13 is expressed as a fusion protein having a peptide (His 6) composed of six histidine residues on the N-terminal side, this fusion protein was purified by affinity chromatography using a metal chelate column.

Several transformants were obtained by transforming E. coli JM109 with each of plasmids pMAL-MDC-(C1), pMAL-MDC(dC1) and pH6-MDC(C1) and selecting for ampicillin resistance.

Example 13 Expression and purification of recombinant MDC proteins

Each of the transformants obtained in Example 12 was grown and the resulting recombinant MDC fusion protein was extracted and purified from the culture.

Specifically, 100 ml of LB medium (1% polypeptone, 0.5% yeast extract, 1% NaCl) was inoculated with each transformant and incubated overnight at 37 • C with shaking. The culture was diluted 10-fold with LB medium previously warmed to 37 • C and incubated for additional 30-90 minutes to obtain a culture in the logarithmic growth phase. To 1 liter of the culture was added IPTG (isopropyl-β-D-thiogalactopyranoside) so as to give a final concentration of 1 mM. This culture was incubated for 3-4 hours and then centrifuged to collect the cells therefrom.

In the case of transformant of plasmid pMAL-MDC(C1) or pMAL-MDC(dC1), the cells were suspended in 10 ml of a column buffer (20 mM Tris-HCl, pH 7.4, 200 mM NaCl) and disintegrated by sonication. Since the recombinant MDC fusion protein was present in the insoluble fraction of the disintegrated cell suspension, this was separated by centrifugation and dissolved in a denaturing buffer (8M urea, 20 mM Tris-HCl, pH 8.5, 10 mM dithiothreitol). Then, this solution was dialyzed against the column buffer and centrifuged to collect a supernatant soluble fraction. The dialyzed insoluble fraction was further denatured, dialyzed and centrifuged repeatedly to collect additional supernatant soluble fractions. The combined soluble fraction was applied to an amylose column (manufactured by New England Biolabs), which was

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washed with the column buffer and eluted with the column buffer containing 10 mM maltose. The eluted fractions were analyzed by absorptiometry at 280 nm and SDS-polyacrylamide electrophoresis (with Coomassie Blue staining), and combined into fractions. As a result, a fraction in which the desired MBP (maltose binding protein) fusion protein (about 68 Kd) was detected as a principal band was obtained for each of the transformants generated with plasmids pMAL-MDC(C1) and pMAL-MDC(dC1). The yield was 46.4 mg and 10.0 mg (when an OD_{280} of 1 was taken as 1 mg/ml), respectively. These fusion proteins will hereinafter be referred to as MBP-MDC(C1) and MBP-MDC(dC1), respectively.

Similarly, in the case of transformant of plasmid pH6-MDC(C1), the cells were suspended in 10 ml of a sonication buffer (10 mM sodium phosphate, pH 8.0, 200 mM NaCl) and disintegrated by sonication. Since the recombinant MDC fusion protein was present in the insoluble fraction of the disintegrated cell suspension, this was separated by centrifugation and dissolved in buffer A (6M guanidine hydrochloride, 100 mM NaH_2PO_4, 10 mM Tris-HCl, PH 8.0). Then, this solution was centrifuged to collect a supernatant soluble fraction, which was applied to a Ni-NTA column (manufactured by Diagen). This column was washed with buffer A and then buffer B (8M urea, 100 mM NaH_2PO_4, 10 mM Trim-HCl, pH 8.0), and eluted stepwise with buffer C (8M urea, 100 mM NaH_2PO_4, 10 mM Tris-HCl, pH 6.3), buffer D (8M urea, 100 mM NaH_2PO_4, 10 mM Tris-HCl, pH 5.9), buffer E (8M urea, 100 mM NaH_2PO_4, 10 mM Tris-HCl, pH 4.5) and buffer F (6M guanidine hydrochloride, 200 mM acetic acid). The eluted fractions were analyzed by absorptiometry at 280 nm and SDS-polyacrylamide electrophoresis (with Coomassie Blue staining), and combined into fractions. As a result, a fraction in which the desired His6 fusion protein (about 34 Kd) was detected as a single band was obtained from the effluent resulting from elution with buffer F. The yield was 51.9 mg (when an OD_{280} of 1 was taken as 1 mg/ml). This fusion protein will hereinafter be referred to as His6-MDC(C1).

Example 14 Preparation of a monoclonal antibody and a rabbit polyclonal antibody

The three recombinant fusion proteins, His6-MDC(C1), MBP-MDC(dC1) and MBP-MDC(C1), obtained in Example 13 were used as an immunizing antigen, an antigen for antibody purification and screening, and a standard antigen for measurement, respectively.

An anti-MDC protein specific monoclonal antibody was prepared by immunizing a mouse with His6-MDC(C1). Specifically, a solution of His6-MDC(C1) (500-1000 μg/ml) in 3 M urea/PBS was mixed with complete adjuvant at a ratio of 1:1, and this mixture was injected into the peritoneal cavity of a mouse at a dose of 100 μg per animal. This injection was repeated 4-6 times at intervals of 2 weeks. After completion of the immunization, hybridomas were produced by fusing P3U1 cells with B cells in the presence of PEG1500. Then, hybridomas productive of an anti-MDC protein specific antibody were selected by monitoring the antibody titer in the culture supernatant.

In order to measure the antibody titer, a first reaction was effected by adding 100 μl of the culture supernatant to a polystyrene cup having a solid phase formed from the MBP-MDC(dC1) fusion protein obtained in Example 13 (5 μg/ml). After washing, a second reaction was effected by the addition of anti-mouse IgG HRP (horse-raddish peroxidase). After washing, a color reaction (third reaction) was effected by the addition of an enzyme substrate solution [i.e., a mixed solution of hydrogen peroxide and ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)]], and the produced color was monitored.

The hybridomas were grown on a 96-well multi-plate and screened by means of HAT medium. After about 2 weeks, clones reacting specifically with the antigen were selected by measuring the antibody titer in the culture supernatant. As a result of further cloning, 3 clones (G1-5A2-2C8, G2-2F2-3D11 and G2-2D10-3F5) were established as antibody-producing hybridomas. The class and subclass of the antibody produced by each of the established clones was IgG_1 for G1-5A2-2C8, IgG_{2b} for G2-2F2-3D11, and IgM for G2-2D10-3F5. 3,000,000 cells of each hybridoma were introduced into the peritoneal cavity of a BALB/c mouse to which 0.5 ml of pristane had been administered intraperitoneally about one week before. After 8-10 days, the ascites was collected. From the ascites collected from each animal, an antibody was purified by affinity chromatography using a protein G column.

Similarly, an anti-MDC protein polyclonal antibody was prepared by immunizing a rabbit with an immunizing antigen comprising His6-MDD(C1) obtained in Example 13.

Specifically, like the mouse, a rabbit was immunized with a mixture prepared by mixing a solution of His6-MDC(C1) (500-1000 μg/ml) in 3 M urea/PBS with complete adjuvant at a ratio of 1:1. After completion of the immunization, an antiserum was obtained and its antibody titer was measured using a polystyrene cup having a solid phase formed from the MBP-MDC(dC1) fusion protein obtained in Example 13. The antiserum was diluted 500- to 64,000-fold, 100 μl each of the dilutions were added to wells, and their antibody titers were tested with goat anti-rabbit IgG-HRP. Thus, the antibody titer was detectable up to the

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64,000-fold dilution. Since no antibody reacting with MBP-MDC(dC1) was present in the serum before immunization, it could be confirmed that an antibody reacting specifically with the protein was produced. Furthermore, this antiserum was purified by affinity chromatography using a protein G column and a Sepharose column having the MBP-MDC(dC1) fusion protein immobilized therein.

A method for the determination of the MDC protein by ELISA using the purified monoclonal antibody and purified rabbit polyclonal antibody obtained in the above-described manner was established.

Specifically, the purified monoclonal antibody derived from a hybridoma (G2-2F2-3D11) was immobilized on a 96-well plate and blocked with BSA (bovine serum albumin). Test solutions containing purified MBP-MDC(C1) at concentrations of 0.156 to 5.00 μg/ml were prepared, added to wells in an amount of 100 μl per well, and reacted at room temperature for an hour. After the wells were washed, a solution (5 μg/ml) of the purified rabbit polyclonal antibody was added in an amount of 100 μl per well and reacted at room temperature for an hour. After the wells were washed, anti-rabbit IgG-HRP (5 μg/ml) was added in an amount of 100 μl per well and reacted at room temperature for an hour. After completion of the reaction, 2 mM sodium azide was added in an amount of 100 μl per well and the absorbances at 405 nm and 490 nm were measured. It was confirmed that the differential absorbances thus obtained were closely correlated with the concentrations of the test solutions, exhibiting an approximately linear relationship in the range of 0 to 2.5 μg/ml (see Fig. 8). This indicates that ELISA using these monoclonal antibody and rabbit polyclonal antibody can be used as a method for the determination of the MDC protein.

BNSDOCID: <EP 0633268A2>

SEQUENCE LISTING

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 488 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
 1               5                  10                  15

Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
            20                  25                  30

Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly
        35                  40                  45

Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro
    50                  55                  60

Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His
65                  70                  75                  80

Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu
                85                  90                  95
```


BNSDOCID: <EP 0633268A2>

```
Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg
            100                 105                 110

Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val
        115                 120                 125

His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
    130                 135                 140

Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala
145                 150                 155                 160

Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn
                165                 170                 175

Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys
            180                 185                 190

Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val
        195                 200                 205

Tyr Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe
    210                 215                 220

Ser Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly
225                 230                 235                 240

Gly Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn
                245                 250                 255

Met Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu
            260                 265                 270

Gly Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys
        275                 280                 285

Pro Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu
    290                 295                 300

Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu
305                 310                 315                 320
```


BNSDOCID: <EP 0633268A2>

Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu
325 330 335

Asp Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys
340 345 350

Asp Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys
355 360 365

Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys
370 375 380

Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala
385 390 395 400

Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln
405 410 415

Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu
420 425 430

Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
435 440 445

Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys
450 455 460

Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser
465 470 475 480

Gly Trp Val Gln Cys Ser Lys Gln
485 488

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 524 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

BNSDOCID: <EP 0633268A2>

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

```
Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg
 1               5                  10                  15

His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp
            20                  25                  30

His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala
        35                  40                  45

Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn
    50                  55                  60

Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala
65                  70                  75                  80

Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro
                85                  90                  95

Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala
            100                 105                 110

Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val
        115                 120                 125

Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu
    130                 135                 140

Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val
145                 150                 155                 160
```


BNSDOCID: <EP 0633268A2>

Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp Val
165 170 175

Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala Met Glu
180 185 190

Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu Leu Glu
195 200 205

Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro Glu Pro
210 215 220

Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln Ser Thr Ser
225 230 235 240

Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser His Gly Gly
245 250 255

Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val Thr Leu Ala
260 265 270

Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys His Arg Ser
275 280 285

Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly Cys Ile Met
290 295 300

Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile
305 310 315 320

Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe
325 330 335

Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly Asn Gly Phe
340 345 350

Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln Glu Cys Ser
355 360 365

Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr His Asp Ala
370 375 380

BNSDOCID: <EP 0633268A2>

Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
385 390 395 400

Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
405 410 415

Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
420 425 430

Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
435 440 445

Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
450 455 460

Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
465 470 475 480

Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Pro
485 490 495

Gln Gln Gly Arg Ala Val Trp Leu Pro Pro Leu Cys Gln His Leu Trp
500 505 510

Ser Ser Ser Ala Arg Gly Pro Gly Gly Arg His Gln
515 520 524

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 670 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

BNSDOCID: <EP 0633268A2>

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg
 1               5                  10                  15

His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp
            20                  25                  30

His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala
        35                  40                  45

Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn
    50                  55                  60

Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala
65                  70                  75                  80

Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro
                85                  90                  95

Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala
            100                 105                 110

Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val
        115                 120                 125

Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu
    130                 135                 140

Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val
145                 150                 155                 160

Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp Val
                165                 170                 175

Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala Met Glu
            180                 185                 190
```


BNSDOCID: <EP 0633268A2>

Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu Leu Glu
195 200 205

Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro Glu Pro
210 215 220

Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln Ser Thr Ser
225 230 235 240

Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser His Gly Gly
245 250 255

Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val Thr Leu Ala
260 265 270

Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys His Arg Ser
275 280 285

Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly Cys Ile Met
290 295 300

Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile
305 310 315 320

Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe
325 330 335

Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly Asn Gly Phe
340 345 350

Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln Glu Cys Ser
355 360 365

Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr His Asp Ala
370 375 380

Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
385 390 395 400

Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
405 410 415

BNSDOCID: <EP 0633268A2>

```
Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
            420                 425                 430

Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
        435                 440                 445

Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
    450                 455                 460

Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
465                 470                 475                 480

Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Asp
                485                 490                 495

Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly Ala Pro Arg
            500                 505                 510

Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe Tyr His Gln
        515                 520                 525

Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu Ala Asp Gly
    530                 535                 540

Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly Pro Asn Met
545                 550                 555                 560

Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe Asn Phe Ser
                565                 570                 575

Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His His Gly Val
            580                 585                 590

Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp Thr Gly Lys
        595                 600                 605

Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro Thr Gly Glu
    610                 615                 620

Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile Ile Gly Ser
625                 630                 635                 640
```


BNSDOCID: <EP 0633268A2>

Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly Gly Thr Gly
645 650 655

Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly Ala
660 665 670

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 769 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Met Arg Leu Leu Arg Arg Trp Ala Phe Ala Ala Leu Leu Leu Ser Leu
1 5 10 15

Leu Pro Thr Pro Gly Leu Gly Thr Gln Gly Pro Ala Gly Ala Leu Arg
20 25 30

Trp Gly Gly Leu Pro Gln Leu Gly Gly Pro Gly Ala Pro Glu Val Thr
35 40 45

Glu Pro Ser Arg Leu Val Arg Glu Ser Ser Gly Gly Glu Val Arg Lys
50 55 60

Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro
65 70 75 80

Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn
85 90 95

BNSDOCID: <EP 0633268A2>

Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr
100 105 110

Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly
115 120 125

Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His
130 135 140

Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser
145 150 155 160

Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro
165 170 175

Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro
180 185 190

Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala
195 200 205

Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys
210 215 220

Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr
225 230 235 240

Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg
245 250 255

Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu
260 265 270

Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val
275 280 285

Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp
290 295 300

Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu
305 310 315 320

BNSDOCID: <EP 0633268A2>

```
Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln
                325                 330                 335

Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser
            340                 345                 350

His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val
        355                 360                 365

Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys
    370                 375                 380

His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly
385                 390                 395                 400

Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg
                405                 410                 415

Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser
            420                 425                 430

Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly
        435                 440                 445

Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln
    450                 455                 460

GGlu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr
465                 470                 475                 480

His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr
                485                 490                 495

Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile
            500                 505                 510

Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His
        515                 520                 525

Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly
    530                 535                 540
```


BNSDOCID: <EP 0633268A2>

```
Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His
545                 550                 555                 560

Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr
                565                 570                 575

Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser
            580                 585                 590

Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly
        595                 600                 605

Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe
    610                 615                 620

Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu
625                 630                 635                 640

Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly
                645                 650                 655

Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe
            660                 665                 670

Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His
        675                 680                 685

His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp
    690                 695                 700

Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro
705                 710                 715                 720

Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile
                725                 730                 735

Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly
            740                 745                 750

Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly
        755                 760                 765
```


BNSDOCID: <EP 0633268A2>

Ala
769

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 1464 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE

(A) NAME/KEY: CDS

(B) LOCATION: 1..1464

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
CTC CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA      48
Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
 1               5                  10                  15

ACC CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG      96
Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
            20                  25                  30

CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG     144
Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly
        35                  40                  45
```


BNSDOCID: <EP 0633268A2>

```
CTG CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC     192
Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro
     50                  55                  60

CAA GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC     240
Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His
 65                  70                  75                  80

CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA     288
Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu
                 85                  90                  95

CCA GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG     336
Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg
            100                 105                 110

CCG AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG     384
Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val
        115                 120                 125

CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG     432
His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
    130                 135                 140

CTG TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC     480
Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala
145                 150                 155                 160

AAG TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC     528
Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn
                165                 170                 175

ACT CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG     576
Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys
            180                 185                 190

ATC CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC     624
Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val
        195                 200                 205
```


BNSDOCID: <EP 0633268A2>

```
TAC CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC     672
Tyr Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe
    210                 215                 220

TCG GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG     720
Ser Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly
225                 230                 235                 240

GGC ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC     768
Gly Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn
                245                 250                 255

ATG GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG     816
Met Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu
            260                 265                 270

GGC ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT     864
Gly Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys
        275                 280                 285

CCA GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG     912
Pro Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu
    290                 295                 300

CCC CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG     960
Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu
305                 310                 315                 320

CAG GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG    1008
Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu
                325                 330                 335

GAC CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC    1056
Asp Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys
            340                 345                 350

GAC TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC    1104
Asp Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys
        355                 360                 365
```


BNSDOCID: <EP 0633268A2>

```
AAG AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC   1152
Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys
    370                 375                 380

TGT CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC   1200
Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala
385                 390                 395                 400

GTG AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG   1248
Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln
                405                 410                 415

TGC CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG   1296
Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu
            420                 425                 430

CAG GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC   1344
Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
        435                 440                 445

CAG GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG   1392
Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys
    450                 455                 460

CTG AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC   1440
Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser
465                 470                 475                 480

GGC TGG GTC CAG TGC AGT AAG CAG                                  1464
Gly Trp Val Gln Cys Ser Lys Gln
                485
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 2923 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

BNSDOCID: <EP 0633268A2>

(ii) MOLECULE TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE

(A) NAME/KEY: 5' UTR

(B) LOCATION: 1..27

(ix) FEATURE

(A) NAME/KEY: 3' UTR

(B) LOCATION: 1600..2923

(ix) FEATURE

(A) NAME/KEY: CDS

(B) LOCATION: 28..1599

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

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GCGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC      51
                              Met Cys Trp Leu Ser His Gln Leu
                               1               5

CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC    99
Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr
     10                  15                  20

CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC   147
Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu
 25                  30                  35                  40

CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG   195
Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu
                 45                  50                  55
```


BNSDOCID: <EP 0633268A2>

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CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA     243
His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln
            60                  65                  70

GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC     291
Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu
        75                  80                  85

ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA     339
Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro
    90                  95                  100

GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG     387
Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro
105                 110                 115                 120

AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC     435
Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His
                125                 130                 135

AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG     483
Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu
            140                 145                 150

TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG     531
Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys
        155                 160                 165

TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT     579
Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr
    170                 175                 180

CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC     627
Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile
185                 190                 195                 200

CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC     675
Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr
                205                 210                 215
```


BNSDOCID: <EP 0633268A2>

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CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG     723
Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser
            220                 225                 230

GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC     771
Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly
        235                 240                 245

ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG     819
Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met
    250                 255                 260

GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC     867
Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
265                 270                 275                 280

ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA     915
Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro
                285                 290                 295

GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC     963
Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro
            300                 305                 310

CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG    1011
Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln
        315                 320                 325

GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC    1059
Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp
    330                 335                 340

CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC    1107
Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp
345                 350                 355                 360

TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG    1155
Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys
                365                 370                 375
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BNSDOCID: <EP 0633268A2>

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AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT   1203
Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys
            380                 385                 390

CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC GTG   1251
Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val
        395                 400                 405

AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC   1299
Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
    410                 415                 420

CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG   1347
Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
425                 430                 435                 440

GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG   1395
Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
                445                 450                 455

GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG   1443
Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
            460                 465                 470

AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC   1491
Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
        475                 480                 485

TGG GTC CAG TGC AGT AAG CAG CCC CAA CAG GGA CGT GCT GTG TGG CTT   1539
Trp Val Gln Cys Ser Lys Gln Pro Gln Gln Gly Arg Ala Val Trp Leu
    490                 495                 500

CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT GGT   1587
Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ser Ala Arg Gly Pro Gly
505                 510                 515                 520

GGG AGA CAT CAG TAGTGTCACC TTCTACCACC AGGGCAAGGA GCTGGACTGC      1639
Gly Arg His Gln
            524

AGGGGAGGCC ACGTGCAGCT GGCGGACGGC TCTGACCTGA GCTATGTGGA GGATGGCACA 1699
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BNSDOCID: <EP 0633268A2>

GCCTGCGGGC CTAACATGTT GTGCCTGGAC CATCGCTGCC TGCCAGCTTC TGCCTTCAAC 1759
TTCAGCACCT GCCCCGGCAG TGGGGAGCGC CGGATTTGCT CCCACCACGG GGTCTGCAGC 1819
AATGAAGGGA AGTGCATCTG TCAGCCAGAC TGGACAGGCA AAGACTGCAG TATCCATAAC 1879
CCCCTGCCCA CGTCCCCACC CACGGGGGAG ACGGAGAGAT ATAAAGGTCC CAGCGGCACC 1939
AACATCATCA TTGGCTCCAT CGCTGGGGCT GTCCTGGTTG CAGCCATCGT CCTGGGCGGC 1999
ACGGGCTGGG GATTTAAAAA CATTCGCCGA GGAAGGTCCG GAGGGGCCTA AGTGCCACCC 2059
TCCTCCCTCC AAGCCTGGCA CCCACCGTCT CGGCCCTGAA CCACGAGGCT GCCCCCATCC 2119
AGCCACGGAG GGAGGCACCA TGCAAATGTC TTCCAGGTCC AAACCCTTCA ACTCCTGGCT 2179
CCGCAGGGGT TTGGGTGGGG GCTGTGGCCC TGCCCTTGGC ACCACCAGGG TGGACCAGGC 2239
CTGGAGGGCA CTTCCTCCAC AGTCCCCCAC CCACCTCCTG CGGCTCAGCC TTGCACACCC 2299
ACTGCCCCGT GTGAATGTAG CTTCCACCTC ATGGATTGCC ACAGCTCAAC TCGGGGGCAC 2359
CTGGAGGGAT GCCCCCAGGC AGCCACCAGT GGACCTAGCC TGGATGGCCC CTCCTTGCAA 2419
CCAGGCAGCT GAGACCAGGG TCTTATCTCT CTGGGACCTA GGGGGACGGG GCTGACATCT 2479
ACATTTTTTA AAACTGAATC TTAATCGATG AATGTAAACT CGGGGGTGCT GGGGCCAGGG 2539
CAGATGTGGG GATGTTTTGA CATTTACAGG AGGCCCCGGA GAAACTGAGG TATGGCCATG 2599
CCCTAGACCC TCCCCAAGGA TGACCACACC CGAAGTCCTG TCACTGAGCA CAGTCAGGGG 2659
CTGGGCATCC CAGCTTGCCC CCGCTTAGCC CCGCTGAGCT TGGAGGAAGT ATGAGTGCTG 2719
ATTCAAACCA AAGCTGCCTG TGCCATGCCC AAGGCCTAGG TTATGGGTAC GGCAACCACA 2779
TGTCCCAGAT CGTCTCCAAT TCGAAAACAA CCGTCCTGCT GTCCCTGTCA GGACACATGG 2839
ATTTTGGCAG GGCGGGGGGG GGTTCTAGAA AATATAGGTT CCTATAATAA AATGGCACCT 2899
TCCCCCTTTA AAAAAAAAAA AAAA 2923

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 2913 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

BNSDOCID: <EP 0633268A2>

(ix) FEATURE

(A) NAME/KEY: 5' UTR

(B) LOCATION: 1..27

(ix) FEATURE

(A) NAME/KEY: 3' UTR

(B) LOCATION: 2038..2913

(ix) FEATURE

(A) NAME/KEY: CDS

(B) LOCATION: 28..2037

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

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GCGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC      51
                              Met Cys Trp Leu Ser His Gln Leu
                               1               5

CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC    99
Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr
     10                  15                  20

CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC   147
Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu
 25                  30                  35                  40

CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG   195
Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu
                 45                  50                  55

CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA   243
His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln
             60                  65                  70

GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC   291
Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu
         75                  80                  85
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BNSDOCID: <EP 0633268A2>

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ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA     339
Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro
     90                  95                 100

GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG     387
Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro
105                 110                 115                 120

AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC     435
Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His
                125                 130                 135

AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG     483
Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu
            140                 145                 150

TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG     531
Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys
        155                 160                 165

TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT     579
Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr
    170                 175                 180

CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC     627
Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile
185                 190                 195                 200

CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC     675
Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr
                205                 210                 215

CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG     723
Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser
            220                 225                 230

GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC     771
Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly
        235                 240                 245
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BNSDOCID: <EP 0633268A2>

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ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG     819
Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met
    250                 255                 260

GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC     867
Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
265                 270                 275                 280

ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA     915
Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro
                285                 290                 295

GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC     963
Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro
            300                 305                 310

CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG    1011
Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln
        315                 320                 325

GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC    1059
Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp
    330                 335                 340

CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC    1107
Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp
345                 350                 355                 360

TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG    1155
Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys
                365                 370                 375

AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT    1203
Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys
            380                 385                 390

CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC GTG    1251
Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val
        395                 400                 405
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BNSDOCID: <EP 0633268A2>

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AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC   1299
Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
    410                 415                 420

CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG   1347
Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
425                 430                 435                 440

GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG   1395
Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
                445                 450                 455

GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG   1443
Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
            460                 465                 470

AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC   1491
Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
        475                 480                 485

TGG GTC CAG TGC AGT AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT   1539
Trp Val Gln Cys Ser Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys
    490                 495                 500

GTC AAC ATC TCT GGA GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC   1587
Val Asn Ile Ser Gly Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile
505                 510                 515                 520

AGT AGT GTC ACC TTC TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA   1635
Ser Ser Val Thr Phe Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly
                525                 530                 535

GGC CAC GTG CAG CTG GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT   1683
Gly His Val Gln Leu Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp
            540                 545                 550

GGC ACA GCC TGC GGG CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG   1731
Gly Thr Ala Cys Gly Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu
        555                 560                 565
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BNSDOCID: <EP 0633268A2>

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CCA GCT TCT GCC TTC AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC   1779
Pro Ala Ser Ala Phe Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg
    570                 575                 580

CGG ATT TGC TCC CAC CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC   1827
Arg Ile Cys Ser His His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile
585                 590                 595                 600

TGT CAG CCA GAC TGG ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG   1875
Cys Gln Pro Asp Trp Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu
                605                 610                 615

CCC ACG TCC CCA CCC ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC   1923
Pro Thr Ser Pro Pro Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser
            620                 625                 630

GGC ACC AAC ATC ATC ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA   1971
Gly Thr Asn Ile Ile Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala
        635                 640                 645

GCC TAC GTC CTG GGC GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA   2019
Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg
    650                 655                 660

GGA AGG TCC GGA GGG GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG          2067
Gly Arg Ser Gly Gly Ala
665                 670

CACCCACCGT CTCGGCCCTG AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC 2127
CATGCAAATG TCTTCCAGGT CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG 2187
GGGCTGTGGC CCTGCCCTTG GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC 2247
ACAGTCCCCC ACCCACCTCC TGCGGCTCAG CCTTGCACAC CCACTGCCCC GTGTGAATGT 2307
AGCTTCCACC TCATGGATTG CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG 2367
GCAGCCACCA GTGGACCTAG CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG 2427
GGTCTTATCT CTCTGGGACC TAGGGGGACG GGGCTGACAT CTACATTTTT TAAAACTGAA 2487
TCTTAATCGA TGAATGTAAA CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT 2547
GACATTTACA GGAGGCCCCG GAGAAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCCAAG 2607
GATGACCACA CCCGAAGTCC TGTCACTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC 2667
CCCCGCTTAG CCCCGCTGAG CTTGGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC 2727
TGTGCCATGC CCAAGGCCTA GGTTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA 2787
ATTCGAAAAC AACCGTCCTG CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG 2847
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BNSDOCID: <EP 0633268A2>

GGGGTTCTAG AAAATATAGG TTCCTATAAT AAAATGGCAC CTTCCCCCTT TAAAAAAAAA AAAAAA 2907 2913

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 3183 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE

(A) NAME/KEY: 3' UTR

(B) LOCATION: 2308..3183

(ix) FEATURE

(A) NAME/KEY: CDS

(B) LOCATION: 1..2307

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

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ATG AGG CTG CTG CGG CGC TGG GCG TTC GCG GCT CTG CTG CTG TCG CTG      48
Met Arg Leu Leu Arg Arg Trp Ala Phe Ala Ala Leu Leu Leu Ser Leu
1               5                  10                  15

CTC CCC ACG CCC GGT CTT GGG ACC CAA GGT ccT GCT GGA GCT CTG Cga      96
Leu Pro Thr Pro Gly Leu Gly Thr Gln Gly Pro Ala Gly Ala Leu Arg
            20                  25                  30
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BNSDOCID: <EP 0633268A2>

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TGG GGG GGC TTA CCC CAG CTG GGA GGC CCA GGA GCC CCT GAG GTC ACG    144
Trp Gly Gly Leu Pro Gln Leu Gly Gly Pro Gly Ala Pro Glu Val Thr
         35                  40                  45

GAA CCC AGC CGT CTG GTT AGG GAG AGC TCC GGG GGA GAG GTC CGA AAG    192
Glu Pro Ser Arg Leu Val Arg Glu Ser Ser Gly Gly Glu Val Arg Lys
     50                  55                  60

CAG CAG CTG GAC ACA AGG GTC CGC CAG GAG CCA CCA GGG GGC CCG CCT    240
Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro
 65                  70                  75                  80

GTC CAT CTG GCC CAG GTG AGT TTC GTC ATC CCA GCC TTC AAC TCA AAC    288
Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn
                 85                  90                  95

TTC ACC CTG GAC CTG GAG CTG AAC CAC CAc CTC CTC TCC TCG CAA TAC    336
Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr
            100                 105                 110

GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GGG    384
Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly
        115                 120                 125

GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC    432
Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His
    130                 135                 140

TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG CAT GGG GTC TTC TCT    480
Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser
145                 150                 155                 160

GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG GTG GCT GGA CCT    528
Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro
                165                 170                 175

TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT    576
Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro
            180                 185                 190
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BNSDOCID: <EP 0633268A2>

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CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA GGC TGC CTG TTT GCT     624
Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala
        195                 200                 205

GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA     672
Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys
    210                 215                 220

AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC AGT GAA ACC AAG TAT     720
Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr
225                 230                 235                 240

GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG TTC GAG CAG ATG CGA     768
Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg
                245                 250                 255

CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG     816
Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu
            260                 265                 270

GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT     864
Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val
        275                 280                 285

GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC     912
Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp
    290                 295                 300

CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG     960
Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu
305                 310                 315                 320

CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG GGC AGG ACC TTC CAG    1008
Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln
                325                 330                 335

AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA TGC TCC CTG TCC    1056
Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser
            340                 345                 350
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CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG GGG GCG ATG GCC GTG   1104
His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val
        355                 360                 365

ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC ATG ATG TGG AAC AAA   1152
Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys
    370                 375                 380

CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA GAC ATC TGG CTG GGC   1200
His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly
385                 390                 395                 400

TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC CGC AAG TTC TCT CGC   1248
Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg
                405                 410                 415

TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG GAG GGT GGT GGC AGC   1296
Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser
            420                 425                 430

TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC CCC CCA GAG TGC GGG   1344
Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly
        435                 440                 445

AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG CAG   1392
Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln
    450                 455                 460

GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG AAA TGC ACC CTG ACT   1440
Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr
465                 470                 475                 480

CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC AAG TAC   1488
His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr
                485                 490                 495

GAA CCA CGG GGT GTG TCC TGC CGA GAG GCC GTG AAC GAG TGC GAC ATC   1536
Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile
            500                 505                 510
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BNSDOCID: <EP 0633268A2>

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GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC CCG CCT AAC CTG CAC   1584
Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His
        515                 520                 525

AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG GGC CGC TGC TAC GGA   1632
Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly
    530                 535                 540

GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG GTT CTT TGG GGC CAT   1680
Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His
545                 550                 555                 560

GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG   1728
Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr
                565                 570                 575

GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC TGG GTC CAG TGC AGT   1776
Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser
            580                 585                 590

AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT GTC AAC ATC TCT GGA   1824
Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly
        595                 600                 605

GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC AGT AGT GTC ACC TTC   1872
Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe
    610                 615                 620

TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA GGC CAC GTG CAG CTG   1920
Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu
625                 630                 635                 640

GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT GGC ACA GCC TGC GGG   1968
Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly
                645                 650                 655

CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG CCA GCT TCT GCC TTC   2016
Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe
            660                 665                 670
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BNSDOCID: <EP 0633268A2>

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AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC CGG ATT TGC TCC CAC   2064
Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His
        675                 680                 685

CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC TGT CAG CCA GAC TGG   2112
His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp
    690                 695                 700

ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG CCC ACG TCC CCA CCC   2160
Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro
705                 710                 715                 720

ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC GGC ACC AAC ATC ATC   2208
Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile
                725                 730                 735

ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA GCC ATC GTC CTG GGC   2256
Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly
            740                 745                 750

GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA GGA AGG TCC GGA GGG   2304
Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly
        755                 760                 765

GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG CACCCACCGT CTCGGCCCTG        2357
Ala
769

AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC CATGCAAATG TCTTCCAGGT 2417
CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG GGGCTGTGGC CCTGCCCTTG 2477
GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC ACAGTCCCCC ACCCACCTCC 2537
TGCGGCTCAG CCTTGCACAC CCACTGCCCC GTGTGAATGT AGCTTCCACC TCATGGATTG 2597
CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG GCAGCCACCA GTGGACCTAG 2657
CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG GGTCTTATCT CTCTGGGACC 2717
TAGGGGGACG GGGCTGACAT CTACATTTTT TAAAACTGAA TCTTAATCGA TGAATGTAAA 2777
CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT GACATTTACA GGAGGCCCCG 2837
GAGAAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCCAAG GATGACCACA CCCGAAGTCC 2897
TGTCACTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC CCCCGCTTAG CCCCGCTGAG 2957
CTTGGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC TGTGCCATGC CCAAGGCCTA 3017
GGTTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA ATTCGAAAAC AACCGTCCTG 3077
CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG GGGGTTCTAG AAAATATAGG 3137
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BNSDOCID: <EP 0633268A2>

TTCCTATAAT AAAATGGCAC CTTCCCCCTT TAAAAAAAAA AAAAAA 3183

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 9278 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) INTERMEDIATE SOURCE:

(A) LIBRARY: human DNA cosmid library

(ix) FEATURE

(A) NAME/KEY: exon 1

(B) LOCATION: 28..44

(ix) FEATURE

(A) NAME/KEY: exon 2

(B) LOCATION: 308..374

(ix) FEATURE

(A) NAME/KEY: exon 3

(B) LOCATION: 909..994

(ix) FEATURE

(A) NAME/KEY: exon 4

(B) LOCATION: 1081..1156

BNSDOCID: <EP 0633268A2>

(ix) FEATURE

(A) NAME/KEY: exon 5

(B) LOCATION: 1591..1657

(ix) FEATURE

(A) NAME/KEY: exon 6

(B) LOCATION: 1725..1792

(ix) FEATURE

(A) NAME/KEY: exon 7

(B) LOCATION: 2182..2256

(ix) FEATURE

(A) NAME/KEY: exon 8

(B) LOCATION: 2339..2410

(ix) FEATURE

(A) NAME/KEY: exon 9

(B) LOCATION: 2588..2754

(ix) FEATURE

(A) NAME/KEY: exon 10

(B) LOCATION: 3248..3332

(ix) FEATURE

(A) NAME/KEY: exon 11

(B) LOCATION: 3445..3535

(ix) FEATURE

(A) NAME/KEY: exon 12

(B) LOCATION: 3645..3696

BNSDOCID: <EP 0633268A2>

(ix) FEATURE

(A) NAME/KEY: exon 13

(B) LOCATION: 4014..4113

(ix) FEATURE

(A) NAME/KEY: exon 14

(B) LOCATION: 4196..4267

(ix) FEATURE

(A) NAME/KEY: exon 15

(B) LOCATION: 4386..4478

(ix) FEATURE

(A) NAME/KEY: exon 16

(B) LOCATION: 4920..5000

(ix) FEATURE

(A) NAME/KEY: exon 17

(B) LOCATION: 5347..5397

(ix) FEATURE

(A) NAME/KEY: exon 18

(B) LOCATION: 5501..5564

(ix) FEATURE

(A) NAME/KEY: exon 19

(B) LOCATION: 5767..5866

(ix) FEATURE

(A) NAME/KEY: exon 20

(B) LOCATION: 6073..6202

BNSDOCID: <EP 0633268A2>

(ix) FEATURE

(A) NAME/KEY: exon 21

(B) LOCATION: 6300..6468

(ix) FEATURE

(A) NAME/KEY: exon 22

(B) LOCATION: 6557..6671

(ix) FEATURE

(A) NAME/KEY: exon 23

(B) LOCATION: 6756..6846

(ix) FEATURE

(A) NAME/KEY: exon 24

(B) LOCATION: 7829..7846

(ix) FEATURE

(A) NAME/KEY: exon 25

(B) LOCATION: 8165..9038

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

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GCGTTTACTG GCAAACCGCA TTTGTAA  ATG TGC TGG CTG AGC CA NNNNNNNNNN    54
                               Met Cys Trp Leu Ser His
                               1               5

NNNNCCAGGT GAGTTTCGTC ATCCAGCCTT CAACTCAAAC TTCACCCTGG ACCTGGAGCT  114
GAACCAGTGA GNGTGGCCTT GAGCCCAAGA GGAAGGGCAG TGGTGGNNNG GGGGAGACAT  174
GGCTAGGGCC TGGCTGCTGG GGGTCTGGGG GTTGGGCCTG GCGAGAGGGG ACCTGGGTCC  234
TGACCTGAGG CGAGCCTAAA GCCCGACCTC ACCTCGCCCG TGACCCCCCT TCCTGCTGCC  294

CCCTCTGTCT CAG C CAA CTC  CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC  344
                 Gln Leu  Leu Ser Ser Gln Tyr Val Glu Arg His Phe
                          10                  15
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BNSDOCID: <EP 0633268A2>

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AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GTGAGTGCCA CTGCTGGGGA      394
Ser Arg Glu Gly Thr Thr Gln His Ser Thr
    20                  25

CCGGGGCCGG GGATGGAAGG GAGGTGCTGT TTCTGTGGTT CTGTGGTCAC AGGTGTAGGG  454
ACAGGTGGCC ACTGGAGATG GGGTCCTGGG CCTGGCCCCT CAGCACCTTC CCTCTCTCCC  514
GACCCAGGAG GCTCTGAGGG TGGACAGTGG GCAGCTTAGT GCATAGGGCC CTGAAGTCCC  574
CTCACTTGGC CCCAGAGCTC TGACCCCCAG CCAGCCCACG TGGGGCCTAC AGGGACACTC  634
GTTCCGAGCA GGCTGCCAGG ATCCNNNNNN NNNNNNATAG ATGACGTGAA GGAGGCCCAG  694
AGGTTCCTAA CCCCAGAGGG CTAGGAACTT GCCCAGGGTG GCACGGCAAA TTAGGAGCAC  754
CAGCCATCTA GAAACAGGCT CCAGAGCCCC AGGNATACCC AGGGATNGTG GCCACCTGCA  814
CACAGGGCAG CTTCAGTGTC CCCCAAAAAG CCTTGAGGCC CATTGGCTGC CCCCGGCCTC  874

ATGCCAGCGT TCTGCTCACT GTTCTGCTCC TTAG GGG GCT GGA GAC CAC TGC TAC  929
                                      Gly Ala Gly Asp His Cys Tyr
                                          30                  35

TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC    977
Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser
                40                  45                  50

ACC TGC CAG GGG CTG CA GTGAGTATGG GGAGGGGCCG GGCAGCTGGG           1024
Thr Cys Gln Gly Leu His
            55

AGAAGCCTCT GGCCCAGGCC TGGGGACGGA GGGGAGCTGC GCCTCTCTCT CCACAG T   1081
GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG   1129
Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu
        60                  65                  70

GTG GCT GGA CCT TGG GGA GCC CCT CAG GTAAGCCCCA CACAACCCCT         1176
Val Ala Gly Pro Trp Gly Ala Pro Gln
    75                  80

TGCCATCCTC TCTGGTGGCC CTGCCAAGCT TGTCCCAACA GCTGTTGCTG CCACCTCTTC 1236
CTCCTCCGGC TCCTCCCTCA GTAACCCCAG CCTCACTGCC CTCTTCAGTG ACCCCAGCTC 1396
TGGTTCCCTC CCTCCTGTGC CCCAGCTCCC CCTGTGCCCC CAGCTCCAAT GTCCCATCTG 1356
TCCCATAAGT GACCTCCCAT TGGGCTCCAA TGTCCTTTGC CCCTGTCTCT CAGGGTGCCC 1416
CCAGGTCTTG ACCCCGGAAT CTGAGCATCT GGGAGATCAG ATCCGACATG GGAGCTGTGG 1476
CCAGTTCTGG GTCACCCCAG GGTGGGGTGG AGGCGAGGGC TGGATCTGGC CCCCGCCAAG 1536
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BNSDOCID: <EP 0633268A2>

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TGGCCTGGAG CAGGCCCAGT TGGCACCCCA AGAACTAATT TCCCCTCATT GCAG GGA   1593
                                                           Gly

CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC   1641
Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu
    85                  90                  95

GGA TGC AGG GAA CCA G GTAAGGGAGG GGAGGGGGGG TGGGGAGGGG CCNGGCTGTG 1697
Gly Cys Arg Glu Pro Gly
    100

CCCCCCTCAC CTGCCCCTCC CCGACAG GC TGC CTG TTT GCT GTG CCT GCC CAG  1750
                                  Cys Leu Phe Ala Val Pro Ala Gln
                                  105             110

TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA AGG CAG           1792
Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln
    115                 120                 125

GTACGGGGGC CCGCACAGAC CTCGGGCTGC AGAGACCTCG GGCTGCAGAG AGACCTCGGC 1852
CGTGGCCCAG AGCAGGAGGG CACCCTCATC TATGGCTGGG GCGAAGGAAG GCTCAGATGG 1912
ATGTGGCTGG GGGCCAGGGA CCGTGTCTGG GAGAAGCCCC CACCCCTTCC CTAATGCTGG 1972
CATCTACAGA GGCCCCATCC TGGGCAAACC GAGGCTGCCT GCCCTCATTC CAAAGCTGAG 2032
GAAGGACAGG ACCCTCTGCC AGTGGGGAGC TGGCACTGTC CCTGGCTGGA GTCCAGACCC 2092
CCCCATCCCC ACCGAGTCTG TTCCTGGCTT GGCCATGAGA TCAGTCAGAC ATGGAAGGGA 2152

CTGATTCCAA GTGCCCACCC ACCCCCCAG GTC CGC CGG GGC CAC CCT ACA GTG   2205
                                Val Arg Arg Gly His Pro Thr Val
                                        130                 135

CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG   2253
His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
                140                 145                 150

CTG GTGAGTGCCA GGGCAGGGAC AGGGCGTGAC ACTGGGAGGC CCCTGAGGAG       2306
Leu

CCTGGCCCTC CTCCCATTCT TCTCTCTCCC AG TTC GAG CAG ATG CGA CAG TCG   2359
                                  Phe Glu Gln Met Arg Gln Ser
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BNSDOCID: <EP 0633268A2>

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GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG GCC GAT   2407
Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp
160                 165                 170                 175

GTG GTAAGCAGCT CTCCCTCCCT CCCTTCCCTC CTCCTCATGC CCCCCCACCC       2460
Val

CACCACACAC ATTAGGGGGC ACTGTCAGCC CCTGGCTCCC ACTTCCTGGA GAGAACAGAC 2520
AGGCCCTCCT CCAGCCCTGG CCCCAACACC CACTCCCACC CTCCAGCCCC CCTCATCTTC 2580

TCCCCAG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT GCC   2629
       Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala
                   180                 185                 190

ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC CTC   2677
Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu
               195                 200                 205

CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG CCT   2725
Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro
           210                 215                 220

GAG CCC AGT AAT GCC ACC CAC CTC TTC TC  GTGAGTCCCC CACCCTGCAC     2774
Glu Pro Ser Asn Ala Thr His Leu Phe Ser
       225                 230

CTCCTGCCAG CCTCTGCTAG TTGCTACAGT GCTTGGGATT ACTTAACACC TGCCCTGTGC 2834
TGGCTGCTCC TCTCAGAGTC TGGGGACTGG GCTCACCTTG CACCTGCCAC CTACCCCCAG 2894
CCACATGCAA CAGCTGGGCA TCATCCCCTG AATCTGAGGT TGATGCCCTT GTCTTAGCCC 2954
TGGTGGTCCT CTTCTGCCTC TCACCTCCCC TTAGTTCTGT CTTTCCCTTC AACTGTCCCN 3014
NNNNNNNNNN NAGAGTGAAA CTCTGTCTCA AAAGAAAAAN AAAANAAAAG AAGAAAAAAA 3074
AGAACCCAAG GAGCGGGGGA AGGGTCTTGC CTGGGGTCAC CAAGGCTGAT GTAAAGGGCC 3134
AGGCTCACCT CCTGAGGAAG GACTCTAGTG TGAGGGGCTC CCCAAGGCCC CACCACCACC 3194

CGGGGAGCCA CAGGGGAGGG CAGAAGCCAT CCTGACAGCG CACTCCCTTC CAG G GGC  3251
                                                              Gly

AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA   3299
Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile
    235                 240                 245
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BNSDOCID: <EP 0633268A2>

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TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG GTGAGCAGTG                3342
Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu
250                 255                 260

GGGGGACATG GCTGGGGTGG CGGCTGAGGG AAAGGGGCTT AGGGGCACGA CGTGCCTGNT 3402
TGGAAGATGT AGACATCTGT GCCCCATCTT CCCCACCCCC AG TAC GGC AAC ATG      3456
                                                 Tyr Gly Asn Met

GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC    3504
Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
265                 270                 275                 280

ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA G GTATCCTCCC CCAGAGGCCC    3555
Met Met Trp Asn Lys His Arg Ser Ser Ala Gly
                285                 290

CCGTGTGGCC CAGCAGCTCT GGAACGGGAG GGTGACAGTG GGAGGGGTGG TCCTTGGCCT 3615

CCCTCATATC CGCCTGGCTC ACCCCTCAG GG GAC TGC AAG TGT CCA GAC ATC      3667
                                  Asp Cys Lys Cys Pro Asp Ile
                                                  295

TGG CTG GGC TGC ATC ATG GAG GAC ACT GG GTGAGTTCTT GGGGACAACC       3716
Trp Leu Gly Cys Ile Met Glu Asp Thr Gly
    300                 305

GGGGGAAGGT CTTGGGCGAG GGGAGTCTTA GAGCGAGCAT TGTTTGGCAG TCTGGACCAG 3776
GGGNNNNNNN NNNNNGAACA CACCTTCCCT TCCAGGCCGG CTTGCGAGTC CCAGGTTCAA 3836
GCGAGGGATG GGAGCGACAA GGGACAAGGC GGAGGATTCT GGTGCAATCC CGGGGCAGAT 3896
CCTCCGCCTC CTCGCGATGG TGACGAAGTC CCCCAGTGTA CCCCCTCCCC AGCCTTGAGA 3956
GGGGTGAGGG TGGGTTGGAG GGGAGCAGCC AGCAGCACCT CCCCTCGCCC TATCCAG G  4014

TTC TAC CTG CCC CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC     4062
Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn
    310                 315                 320

CAG TTT CTG CAG GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC    4110
Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu
325                 330                 335                 340
```


BNSDOCID: <EP 0633268A2>

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AAG GTACCAGCCC CGCGGCGGGG AGCATGGGAG CGGGCCCTGG GCGGGGTCCG          4163
Lys

GGCCAGACTC CCGACCTGTC CTCCCGGTCC AG CTC CTG GAC CCC CCA GAG TGC    4216
                                  Leu Leu Asp Pro Pro Glu Cys
                                      345

GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG    4264
Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val
    350                 355                 360

CAG GTGAGCGGTG GTGCGGGCGC CAGGTGGGGA ACCGGGATGC GGGGGTGGGC         4317
Gln
365

ACCAGGGAGC GTCTGAGTGG GAGGATTAGG GCTCGCCCGC CTCCTTCCCC TCCTCCCGCG 4377

TCCCTCAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG AAA TGC ACC    4427
        Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr
                        370                 375

CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC    4475
Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys
380                 385                 390                 395

AAG GTAAGCAGGA CCGGCCGGGA GGCGGGGCCA GGACGCAGGA GGAGCGATTG         4528
Lys

GAGGCCTTCA TATAAGGGGT GGGAGCTAGG GAGGGAAGCG GAGCCTTCGG GGACGAAGGC 4588
CTCTGGGGCA GGGCTTGATG CGAAGACAGC GCCAATGGGA GCAAGGGCGG GCTGAAGGAT 4648
GTTGAAGGCN NNNNNNNNNN NNNCGGACGG GAAGCTCCCA GAATCAAGGA GGGCGGGAAG 4708
GTGGGCGGGC TTGGGGCGGT GCTGAGTGCG CTGGGAGCGA GGTGGGGAGC GTTCAAGAGG 4768
TGGTGGGAGC AGGGAAATAA GAACAGGCCT AAACGGGGCC CTGGGGAGCT GGAGGGCCCG 4828
GGGATGTGGG GGTCCAGAGA GCGGGGGGCC TGGGGAGGGC AGGGCCGAGG CATCCATCCT 4888

GCCTGACTCG AGGAGCGCGT CTCTTCCCTA G TAC GAA CCA CGG GGT GTG TCC      4940
                                  Tyr Glu Pro Arg Gly Val Ser
                                      400
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BNSDOCID: <EP 0633268A2>

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TGC CGA GAG GCC GTG AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG   4988
Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly
    405                 410                 415

GAC TCT AGC CAG GTCCGCCCGG CCCCGCCGTC TTGTGGAGCC CTGGGCGAGG       5040
Asp Ser Ser Gln
420

CAACCCCTAC CCTTGTCGAT TTGGTTTTCC CGGACGAGTG CTCAGCACTC CCCTCCTCTC 5100
CACAGCTGGC ATCGACCTTC ACTGATCAGA CTGTTTTCTT ATCTGAGAAA GGGGTTCTTC 5160
ATGCTCCTGG CCTTGTTCCT TCAATCATTA AACCAGAATG TATCGTCTGG CTGGTATCCC 5220
AGCGCCTGGG CCCGGTGNNN NNNNNNNNTA CCCAGATTCC TCCTGGGCAG CCCTCAGCTC 5280
CAGTCCTGGG CAGCCCTCAG CCCAGTCCTG GGACTGCTCC GCTCAACCCC ACCCCTCTCT 5340

CCACAG TGC CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC     5388
      Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp
          425                 430                 435

CAT GAG CAG GTATGATGGC TGCCCCCTGA GCCTGGGATT CAGGGCAGTC           5437
His Glu Gln
       440

TCTTATCTCC ACTCTGACCA CTCAGCATCT CCATCCCTTG CCTCTTAATT CTTGGACTCT 5497

CAG GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC   5545
    Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
                    445                 450                 455

CAG GTT CTT TGG GGC CAT G GTGAGTCTGC TAGGGCTGGA GTGGGACTCC       5594
Gln Val Leu Trp Gly His Ala
                460

GGAGGAGCCC AGAGCTGAGA AGCTGGGGAG AGTGGGTTCC AGCTGAACAG GCCCCCAAGT 5654
GTGTAGCTCC CCAGGATCTC AGGGAGCCCA GGCAGAGTGT GGGAGATGCA GGCCTGAGGT 5714

CTTGGGGTGG GTCCTGGGGC ACGTGGGGTC ACTTGGCATC CTCTCCCCAC AG CG GCT  5771
                                                              Ala

GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG GAG CGT   5819
Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg
    465                 470                 475
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BNSDOCID: <EP 0633268A2>

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Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln
480                 485                 490                 495

GTGAGTACTG AGGCTCCCAG AGGGCCTCTC AGCTCCAGGG CAGGTGTGAG ACTTTTCAGA 5926
GATGGGGTAG TAGGTTCTCC CAGGAGGAGC CTGTCAGTCC CAATGGGCGG GCACGTGGCA 5986
AATGAGGTGG CAGGGTGCAG GGTGAGGGCA GATTAGAGTT CAGTAGTTGA GTCTGAGGTC 6046

AAACTTGGGG CTCACTGTCT CTATAT G CCC CAA CAG GGA CGT GCT GTG TGG    6097
                              Pro Gln Gln Gly Arg Ala Val Trp
                                                  500

CTT CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT   6145
Leu Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ser Ala Arg Gly Pro
    505                 510                 515

GGT GGG AGA CAT CAG TAGTGTCACC TTCTACCACC AGGGCAAGGA GCTGGACTGC   6200
Gly Gly Arg His Gln
520

AGGTGCTGAC CAGCACCAAA ACTCAGGGAG GGGACCTGGC AGCTGTGCTG GGGGTTAGAA 6260
GATCTGGGGG CTGGAGGCTG GGCTGTGTCA CTTCCCCAGG GGAGGCCACG TGCAGCTGGC 6320
GGACGGCTCT GACCTGAGCT ATGTGGAGGA TGGCACAGCC TGCGGGCCTA ACATGTTGTG 6380
CCTGGACCAT CGCTGCCTGC CAGCTTCTGC CTTCAACTTC AGCACCTGCC CCGGCAGTGG 6440
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GCAGCAATGA AGGGAAGTGC ATCTGTCAGC CAGACTGGAC AGGCAAAGAC TGCAGTATCC 6620
ATAACCCCCT GCCCACGTCC CCACCCACGG GGGAGACGGA GAGATATAAA GGTGAGGCTG 6680
GAGCTGGCCG AGGGGGGTCT GTCTGTCCCG CTCTCTATGC CTGTCCTTGC CAGCTAAGCC 6740
CTGCCATCCT CCCAGGTCCC AGCGGCACCA ACATCATCAT TGGCTCCATC GCTGGGGCTG 6800
TCCTGGTTGC AGCCATCGTC CTGGGCGGCA CGGGCTGGGG ATTTAAGTAA GAGACACACA 6860
CACCCTGTGC CCCCTGGCAT CCTTGAGGGG GGATCAGAAT CCCTACTGGT GGAGCTGAGG 6920
GGGCCCTCCC TGAAAGCCCA ACTGAACCAG AGCTCACACG TCATAGGTCC AAGTAGCCTG 6980
CAGGGCTTAA CATTTAGAAA CTAGGAGATT TTAGGCTAGA TGAGGTGCTC ACGCCTGTAA 7040
TCCCAGCACT TTGGGAGGCC AAGGCAGGCG GATCACCTGA GGTCAGGAAT TCAAGACCAG 7100
TCTGGCCAAC ATGGTGAAAC CCGTCTCTAT TAAAAATACA AAAATTAGCC AGCCATGGTG 7160
GTGCACACCT GTAATCCCAG CTACTTGCGA GGCTGAGGCA GAGAATTGCT TGAACCCGGG 7220
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AAAAGAGAAA AGAAATCAGG AGATTTTACA CTAGCAATTC GGATTTCCAG CTCTGGAAAC 7400
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BNSDOCID: <EP 0633268A2>

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 10 7487

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P,X	CANCER RESEARCH, vol. 53, 15 July 1993, MD US, pages 3382-3385, XP002036048 H.SAITO ET AL.: "Detailed deletion mapping of chromosome 17q in ovarian and breast cancers:2-cM region on 17q21.3 is often and commonly deleted in tumors" * the whole document *	8-14	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	31 July 1997	Cupido, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

BNSDOCID: <EP 0633268A3>

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AGAGGGAGGA ACCCACGGCC CAAGGTCACA TGATTGAGTT AGTAGCAGAG TCAGAGCTGG 7640
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CAGGCCCCGG GGACCCCGGC CCCGCTCTGG GGCAAGGGGT CGCATGGCAG CCAAAGGCCC 7760
CTCCCTGAGA GAAGCAAAAG GTCAGATGTC TCCTTTTCCT CTCCCCTTCC ACCATCCTCC 7820
CCCTGCAGAA ACATTCGCCG AGGAAGGTAC GACCCGACCC AGCTGGGGGC AGTGTGATGC 7880
CGGCCACGTC ATCCCTCCCG CTGTCCTTGT CTCCTCCATC TCATTCGTCA CCCGCGTTCT 7940
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TCTTCCATAT CACCACTGTC TGACCTCCCG CAGATCCCTT CCCTGGCCAG CCTGTGACTT 8060
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CCCCCATCCA GCCACGGAGG GAGGCACCAT GCAAATGTCT TCCAGGTCCA AACCCTTCAA 8300
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GACACATGGA TTTTGGCAGG GCGGGGGGGG GTTCTAGAAA ATATAGGTTC CTATAATAAA 9020
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GGCTGGATAT GGGTGGGACA TGAGACTTCC TGTGACCAGC CACCCTGGCT CCCAGCTCTC 9140
TGTATCCTCC TGCCCCGCCC TGGGGGGTGC CTACCCTGGN AGAACCCAGG GAGGAGTGGA 9200
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GGGAGGCAGG GCCAGGAG 9278

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 17 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

BNSDOCID: <EP 0633268A2>

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GCACCTGCCC CGGCAGT 17

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CCAGGACAGC CCCAGCGATG 20

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GGCTGCTGAT CGCTTCTGCT AC 22

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

BNSDOCID: <EP 0633268A2>

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

GAGAAGCTGA ATGTGGAGGG 20

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 19 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GTCAGAGCCG TCCGCCAGC 19

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GCCATCCTCC ACATAGCTCA GG 22

BNSDOCID: <EP 0633268A2>

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

GATGTAAGTC AAGTTCCCAT CAGAGA 26

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

AACAGCTGGT GGTCGTTGAT CACAA 25

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

BNSDOCID: <EP 0633268A2>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

ATGAGGCTGC TGCGGCGCTG 20

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CACAGATCTG GGGGCATATG CTCCCTG 27

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

AACAAGCTTC TACTGATGTC TCCCACC 27

BNSDOCID: <EP 0633268A2>

SEQUENCE LISTING

Reference: 61 826 / u6

Date: May 13, 1994

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: (1) CANCER INSTITUTE

(2) EISAI CO., LTD.

(B) STREET: (1) 37-1, Kamiikebururo 1-chome Toshima-ku

(2) 6-10, Koishikawa 4-chome, Bunkyo-ku

(C) CITY: Tokyo

(D) STATE:

(E) COUNTRY: Japan

(ii) TITLE OF INVENTION: MDC PROTEINS AND DNAs ENCODING THE SAME

(iii) NUMBER OF SEQUENCES: 20

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 488 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

BNSDOCID: <EP 0633268A2>

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Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
 1               5                  10                  15
Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
            20                  25                  30
Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly
        35                  40                  45
Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro
    50                  55                  60
Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His
65                  70                  75                  80
Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu
                85                  90                  95
Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg
            100                 105                 110
Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val
        115                 120                 125
His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
    130                 135                 140
Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala
145                 150                 155                 160
Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn
                165                 170                 175
Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys
            180                 185                 190
Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val
        195                 200                 205
Tyr Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe
    210                 215                 220
Ser Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly
225                 230                 235                 240
Gly Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn
                245                 250                 255
Met Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu
            260                 265                 270
Gly Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys
```


BNSDOCID: <EP 0633268A2>

```
        275                 280                 285
Pro Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu
    290                 295                 300
Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu
305                 310                 315                 320
Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu
                325                 330                 335
Asp Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys
            340                 345                 350
Asp Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys
        355                 360                 365
Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys
    370                 375                 380
Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala
385                 390                 395                 400
Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln
                405                 410                 415
Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu
            420                 425                 430
Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
        435                 440                 445
Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys
    450                 455                 460
Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser
465                 470                 475                 480
Gly Trp Val Gln Cys Ser Lys Gln
                485         488
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 524 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

BNSDOCID: <EP 0633268A2>

(ii) MOLECULAR TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg
 1               5                  10                  15
His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp
            20                  25                  30
His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala
        35                  40                  45
Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn
    50                  55                  60
Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala
65                  70                  75                  80
Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro
                85                  90                  95
Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala
            100                 105                 110
Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val
        115                 120                 125
Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu
    130                 135                 140
Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val
145                 150                 155                 160
Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp Val
                165                 170                 175
Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala Met Glu
            180                 185                 190
Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu Leu Glu
        195                 200                 205
Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro Glu Pro
    210                 215                 220
Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln Ser Thr Ser
225                 230                 235                 240
Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser His Gly Gly
                245                 250                 255
Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val Thr Leu Ala
```


BNSDOCID: <EP 0633268A2>

260 265 270
Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys His Arg Ser
275 280 285
Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly Cys Ile Met
290 295 300
Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile
305 310 315 320
Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe
325 330 335
Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly Asn Gly Phe
340 345 350
Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln Glu Cys Ser
355 360 365
Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr His Asp Ala
370 375 380
Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
385 390 395 400
Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
405 410 415
Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
420 425 430
Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
435 440 445
Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
450 455 460
Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
465 470 475 480
Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Asp
485 490 495
Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly Ala Pro Arg
500 505 510
Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe Tyr His Gln
515 520 525
Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu Ala Asp Gly
530 535 540
Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly Pro Asn Met

BNSDOCID: <EP 0633268A2>

```
Met Cys Trp Leu Ser His Gln Leu Leu Ser Ser Gln Tyr Val Glu Arg
 1               5                  10                  15
His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly Ala Gly Asp
            20                  25                  30
His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala
        35                  40                  45
Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser Asp Gly Asn
    50                  55                  60
Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro Trp Gly Ala
65                  70                  75                  80
Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro
                85                  90                  95
Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala Val Pro Ala
            100                 105                 110
Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln Val
        115                 120                 125
Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr Val Glu Leu
    130                 135                 140
Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg Gln Ser Val
145                 150                 155                 160
Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp Val
                165                 170                 175
Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala Met Glu
            180                 185                 190
Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu Leu Glu
        195                 200                 205
Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro Glu Pro
    210                 215                 220
Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln Ser Thr Ser
225                 230                 235                 240
Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser His Gly Gly
                245                 250                 255
Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val Thr Leu Ala
            260                 265                 270
Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys His Arg Ser
        275                 280                 285
```


BNSDOCID: <EP 0633268A2>

```
Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly Cys Ile Met
    290                 295                 300
Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile
305                 310                 315                 320
Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe
                325                 330                 335
Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly Asn Gly Phe
            340                 345                 350
Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln Glu Cys Ser
        355                 360                 365
Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr His Asp Ala
    370                 375                 380
Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr Glu Pro Arg
385                 390                 395                 400
Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr
                405                 410                 415
Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His Lys Leu Asp
            420                 425                 430
Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly Gly Arg Cys
        435                 440                 445
Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His Ala Ala Ala
    450                 455                 460
Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg Gly
465                 470                 475                 480
Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser Lys Gln Pro
                485                 490                 495
Gln Gln Gly Arg Ala Val Trp Leu Pro Pro Leu Cys Gln His Leu Trp
            500                 505                 510
Ser Ser Ser Ala Arg Gly Pro Gly Gly Arg His Gln
        515                 520             524
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 670 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

BNSDOCID: <EP 0633268A2>

```
545                 550                 555                 560
Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe Asn Phe Ser
                565                 570                 575
Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His His Gly Val
            580                 585                 590
Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp Thr Gly Lys
        595                 600                 605
Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro Thr Gly Glu
    610                 615                 620
Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile Ile Gly Ser
625                 630                 635                 640
Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly Gly Thr Gly
                645                 650                 655
Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly Ala
            660                 665                 670
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 769 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
Met Arg Leu Leu Arg Arg Trp Ala Phe Ala Ala Leu Leu Leu Ser Leu
1               5                  10                  15
Leu Pro Thr Pro Gly Leu Gly Thr Gln Gly Pro Ala Gly Ala Leu Arg
            20                  25                  30
Trp Gly Gly Leu Pro Gln Leu Gly Gly Pro Gly Ala Pro Glu Val Thr
        35                  40                  45
Glu Pro Ser Arg Leu Val Arg Glu Ser Ser Gly Gly Glu Val Arg Lys
    50                  55                  60
Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro
65                  70                  75                  80
Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn
                85                  90                  95
```


BNSDOCID: <EP 0633268A2>

```
Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr
                100                 105                 110
Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly
            115                 120                 125
Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His
        130                 135                 140
Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser
145                 150                 155                 160
Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro
                165                 170                 175
Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro
            180                 185                 190
Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala
        195                 200                 205
Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys
    210                 215                 220
Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr
225                 230                 235                 240
Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg
                245                 250                 255
Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu
            260                 265                 270
Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val
        275                 280                 285
Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp
    290                 295                 300
Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu
305                 310                 315                 320
Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln
                325                 330                 335
Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser
            340                 345                 350
His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val
        355                 360                 365
Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys
    370                 375                 380
```


BNSDOCID: <EP 0633268A2>

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                35                  40                  45
CTG CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC    192
Leu His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro
     50                  55                  60
CAA GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC    240
Gln Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His
 65                  70                  75                  80
CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA    288
Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu
                 85                  90                  95
CCA GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG    336
Pro Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg
            100                 105                 110
CCG AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG    384
Pro Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val
        115                 120                 125
CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG    432
His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
    130                 135                 140
CTG TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC    480
Leu Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala
145                 150                 155                 160
AAG TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC    528
Lys Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn
                165                 170                 175
ACT CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG    576
Thr Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys
            180                 185                 190
ATC CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC    624
Ile Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val
        195                 200                 205
TAC CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC    672
Tyr Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe
    210                 215                 220
TCG GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG    720
Ser Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly
```


BNSDOCID: <EP 0633268A2>

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225                 230                 235                 240
GGC ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC   768
Gly Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn
                245                 250                 255
ATG GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG   816
Met Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu
            260                 265                 270
GGC ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT   864
Gly Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys
        275                 280                 285
CCA GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG   912
Pro Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu
    290                 295                 300
CCC CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG   960
Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu
305                 310                 315                 320
CAG GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG  1008
Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu
                325                 330                 335
GAC CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC  1056
Asp Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys
            340                 345                 350
GAC TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC  1104
Asp Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys
        355                 360                 365
AAG AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC  1152
Lys Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys
    370                 375                 380
TGT CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC  1200
Cys Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala
385                 390                 395                 400
GTG AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG  1248
Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln
                405                 410                 415
TGC CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG  1296
Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu
```


BNSDOCID: <EP 0633268A2>

```
                420                 425                 430
CAG GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC   1344
Gln Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
        435                 440                 445
CAG GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG   1392
Gln Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys
    450                 455                 460
CTG AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC   1440
Leu Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser
465                 470                 475                 480
GGC TGG GTC CAG TGC AGT AAG CAG                                  1464
Gly Trp Val Gln Cys Ser Lys Gln
                485
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2923 base pairs

(B) TYPE: nucleic acid

(C) STRANDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) IMMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE:

(A) NAME/KEY: 5'UTR

(B) LOCATION: 1..27

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 28..1599

(ix) FEATURE:

(A) NAME/KEY: 3'UTR

(B) LOCATION: 1600..2923

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

BNSDOCID: <EP 0633268A2>

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GCGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC        51
                              Met Cys Trp Leu Ser His Gln Leu
                                1               5
CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC      99
Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr
     10                  15                  20
CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC     147
Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu
 25                  30                  35                  40
CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG     195
Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu
                 45                  50                  55
CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA     243
His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln
             60                  65                  70
GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC     291
Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu
         75                  80                  85
ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA     339
Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro
     90                  95                 100
GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG     387
Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro
105                 110                 115                 120
AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC     435
Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His
                125                 130                 135
AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG     483
Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu
            140                 145                 150
TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG     531
Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys
        155                 160                 165
TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT     579
Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr
    170                 175                 180
```


BNSDOCID: <EP 0633268A2>

```
His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly
385                 390                 395                 400
Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg
                405                 410                 415
Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser
            420                 425                 430
Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly
        435                 440                 445
Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln
    450                 455                 460
GGlu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr
465                 470                 475                 480
His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr
                485                 490                 495
Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile
            500                 505                 510
Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His
        515                 520                 525
Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly
    530                 535                 540
Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His
545                 550                 555                 560
Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr
                565                 570                 575
Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser
            580                 585                 590
Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly
        595                 600                 605
Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe
    610                 615                 620
Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu
625                 630                 635                 640
Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly
                645                 650                 655
Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe
            660                 665                 670
```


BNSDOCID: <EP 0633268A2>

```
Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His
        675                 680                 685
His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp
    690                 695                 700
Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro
705                 710                 715                 720
Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile
                725                 730                 735
Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly
            740                 745                 750
Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly
        755                 760                 765
Ala
769
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1464 base pairs

(B) TYPE: nucleic acid

(C) STRANDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: cDNA to mRNA

(xi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) IMMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
CTC CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA     48
Leu Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr
  1               5                  10                  15
ACC CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG     96
Thr Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys
            20                  25                  30
CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG    144
Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly
```


BNSDOCID: <EP 0633268A2>

```
CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC     627
Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile
185                 190                 195                 200
CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC     675
Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr
                205                 210                 215
CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG     723
Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser
            220                 225                 230
GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC     771
Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly
        235                 240                 245
ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG     819
Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met
    250                 255                 260
GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC     867
Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
265                 270                 275                 280
ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA     915
Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro
                285                 290                 295
GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC     963
Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro
            300                 305                 310
CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG    1011
Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln
        315                 320                 325
GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC    1059
Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp
    330                 335                 340
CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC    1107
Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp
345                 350                 355                 360
TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG    1155
Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys
                365                 370                 375
```


BNSDOCID: <EP 0633268A2>

```
AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT   1203
Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys
            380                 385                 390
CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC GTG   1251
Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val
        395                 400                 405
AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC   1299
Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
    410                 415                 420
CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG   1347
Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
425                 430                 435                 440
GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG   1395
Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
                445                 450                 455
GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG   1443
Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
            460                 465                 470
AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC   1491
Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
        475                 480                 485
TGG GTC CAG TGC AGT AAG CAG CCC CAA CAG GGA CGT GCT GTG TGG CTT   1539
Trp Val Gln Cys Ser Lys Gln Pro Gln Gln Gly Arg Ala Val Trp Leu
    490                 495                 500
CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT GGT   1587
Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ser Ala Arg Gly Pro Gly
505                 510                 515                 520
GGG AGA CAT CAG TAGTGTCACC TTCTACCACC AGGGCAAGGA GCTGGACTGC      1639
Gly Arg His Gln
AGGGGAGGCC ACGTGCAGCT GGCGGACGGC TCTGACCTGA GCTATGTGGA GGATGGCACA 1699
GCCTGCGGGC CTAACATGTT GTGCCTGGAC CATCGCTGCC TGCCAGCTTC TGCCTTCAAC 1759
TTCAGCACCT GCCCCGGCAG TGGGGAGCGC CGGATTTGCT CCCACCACGG GGTCTGCAGC 1819
AATGAAGGGA AGTGCATCTG TCAGCCAGAC TGGACAGGCA AAGACTGCAG TATCCATAAC 1879
CCCCTGCCCA CGTCCCCACC CACGGGGGAG ACGGAGAGAT ATAAAGGTCC CAGCGGCACC 1939
AACATCATCA TTGGCTCCAT CGCTGGGGCT GTCCTGGTTG CAGCCATCGT CCTGGGCGGC 1999
ACGGGCTGGG GATTTAAAAA CATTCGCCGA GGAAGGTCCG GAGGGGCCTA AGTGCCACCC 2059
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BNSDOCID: <EP 0633268A2>

TCCTCCCTCC AAGCCTGGCA CCCACCGTCT CGGCCCTGAA CCACGAGGCT GCCCCCATCC 2119
AGCCACGGAG GGAGGCACCA TGCAAATGTC TTCCAGGTCC AAACCCTTCA ACTCCTGGCT 2179
CCGCAGGGGT TTGGGTGGGG GCTGTGGCCC TGCCCTTGGC ACCACCAGGG TGGACCAGGC 2239
CTGGAGGGCA CTTCCTCCAC AGTCCCCCAC CCACCTCCTG CGGCTCAGCC TTGCACACCC 2299
ACTGCCCCGT GTGAATGTAG CTTCCACCTC ATGGATTGCC ACAGCTCAAC TCGGGGGCAC 2359
CTGGAGGGAT GCCCCCAGGC AGCCACCAGT GGACCTAGCC TGGATGGCCC CTCCTTGCAA 2419
CCAGGCAGCT GAGACCAGGG TCTTATCTCT CTGGGACCTA GGGGGACGGG GCTGACATCT 2479
ACATTTTTTA AAACTGAATC TTAATCGATG AATGTAAACT CGGGGGTGCT GGGGCCAGGG 2539
CAGATGTGGG GATGTTTTGA CATTTACAGG AGGCCCCGGA GAAACTGAGG TATGGCCATG 2599
CCCTAGACCC TCCCCAAGGA TGACCACACC CGAAGTCCTG TCACTGAGCA CAGTCAGGGG 2659
CTGGGCATCC CAGCTTGCCC CCGCTTAGCC CCGCTGAGCT TGGAGGAAGT ATGAGTGCTG 2719
ATTCAAACCA AAGCTGCCTG TGCCATGCCC AAGGCCTAGG TTATGGGTAC GGCAACCACA 2779
TGTCCCAGAT CGTCTCCAAT TCGAAAACAA CCGTCCTGCT GTCCCTGTCA GGACACATGG 2839
ATTTTGGCAG GGCGGGGGGG GGTTCTAGAA AATATAGGTT CCTATAATAA AATGGCACCT 2899
TCCCCCTTTA AAAAAAAAAA AAAA 2923

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2913 base pairs

(B) TYPE: nucleic acid

(C) STRANDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) IMMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE:

(A) NAME/KEY: 5'UTR

(B) LOCATION: 1..27

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 28..2037

(ix) FEATURE:

(A) NAME/KEY: 3'UTR

(B) LOCATION: 2038..2913

BNSDOCID: <EP 0633268A2>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

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GCGTTTACTG GCAAACCGCA TTTGTAA ATG TGC TGG CTG AGC CAC CAA CTC        51
                              Met Cys Trp Leu Ser His Gln Leu
                                1               5

CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC      99
Leu Ser Ser Gln Tyr Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr
     10                  15                  20

CAG CAC AGC ACC GGG GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC     147
Gln His Ser Thr Gly Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu
 25                  30                  35                  40

CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG     195
Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu
                  45                  50                  55

CAT GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA     243
His Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln
             60                  65                  70

GAG GTG GCT GGA CCT TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC     291
Glu Val Ala Gly Pro Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu
         75                  80                  85

ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA     339
Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro
     90                  95                 100

GGC TGC CTG TTT GCT GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG     387
Gly Cys Leu Phe Ala Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro
105                 110                 115                 120

AGG CTG AGA AGG AAA AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC     435
Arg Leu Arg Arg Lys Arg Gln Val Arg Arg Gly His Pro Thr Val His
                 125                 130                 135

AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG     483
Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln Leu
            140                 145                 150

TTC GAG CAG ATG CGA CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG     531
Phe Glu Gln Met Arg Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys
        155                 160                 165

TCC GTG GTG AAC CTG GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT     579
```


BNSDOCID: <EP 0633268A2>

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Ser Val Val Asn Leu Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr
    170                 175                 180
CGC ATC GTC CTG GTT GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC   627
Arg Ile Val Leu Val Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile
185                 190                 195                 200
CAG GTG CAG GAT GAC CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC   675
Gln Val Gln Asp Asp Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr
                205                 210                 215
CGA CGG GAG GGT CTG CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG   723
Arg Arg Glu Gly Leu Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser
            220                 225                 230
GGC AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC   771
Gly Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly
        235                 240                 245
ATA TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG   819
Ile Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met
    250                 255                 260
GGG GCG ATG GCC GTG ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC   867
Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
265                 270                 275                 280
ATG ATG TGG AAC AAA CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA   915
Met Met Trp Asn Lys His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro
                285                 290                 295
GAC ATC TGG CTG GGC TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC   963
Asp Ile Trp Leu Gly Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro
            300                 305                 310
CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG  1011
Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln
        315                 320                 325
GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC  1059
Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp
    330                 335                 340
CCC CCA GAG TGC GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC  1107
Pro Pro Glu Cys Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp
345                 350                 355                 360
TGC GGC TCG GTG CAG GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG  1155
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BNSDOCID: <EP 0633268A2>

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Cys Gly Ser Val Gln Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys
                365                 370                 375
AAA TGC ACC CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT   1203
Lys Cys Thr Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys
            380                 385                 390
CGC CGC TGC AAG TAC GAA CCA CGG GGT GTG TCc TGC CGA GAG GCC GTG   1251
Arg Arg Cys Lys Tyr Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val
        395                 400                 405
AAC GAG TGC GAC ATC GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC   1299
Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys
    410                 415                 420
CCG CCT AAC CTG CAC AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG   1347
Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln
425                 430                 435                 440
GGC CGC TGC TAC GGA GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG   1395
Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln
                445                 450                 455
GTT CTT TGG GGC CAT GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG   1443
Val Leu Trp Gly His Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu
            460                 465                 470
AAT GTG GAG GGG ACG GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC   1491
Asn Val Glu Gly Thr Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly
        475                 480                 485
TGG GTC CAG TGC AGT AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT   1539
Trp Val Gln Cys Ser Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys
    490                 495                 500
GTC AAC ATC TCT GGA GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC   1587
Val Asn Ile Ser Gly Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile
505                 510                 515                 520
AGT AGT GTC ACC TTC TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA   1635
Ser Ser Val Thr Phe Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly
                525                 530                 535
GGC CAC GTG CAG CTG GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT   1683
Gly His Val Gln Leu Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp
            540                 545                 550
GGC ACA GCC TGC GGG CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG   1731
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BNSDOCID: <EP 0633268A2>

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Gly Thr Ala Cys Gly Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu
        555                 560                 565
CCA GCT TCT GCC TTC AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC   1779
Pro Ala Ser Ala Phe Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg
    570                 575                 580
CGG ATT TGC TCC CAC CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC   1827
Arg Ile Cys Ser His His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile
585                 590                 595                 600
TGT CAG CCA GAC TGG ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG   1875
Cys Gln Pro Asp Trp Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu
                605                 610                 615
CCC ACG TCC CCA CCC ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC   1923
Pro Thr Ser Pro Pro Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser
            620                 625                 630
GGC ACC AAC ATC ATC ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA   1971
Gly Thr Asn Ile Ile Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala
        635                 640                 645
GCC TAC GTC CTG GGC GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA   2019
Ala Ile Val Leu Gly Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg
    650                 655                 660
GGA AGG TCC GGA GGG GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG         2067
Gly Arg Ser Gly Gly Ala
665                 670
CACCCACCGT CTCGGCCCTG AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC 2127
CATGCAAATG TCTTCCAGGT CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG 2187
GGGCTGTGGC CCTGCCCTTG GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC 2247
ACAGTCCCCC ACCCACCTCC TGCGGCTCAG CCTTGCACAC CCACTGCCCC GTGTGAATGT 2307
AGCTTCCACC TCATGGATTG CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG 2367
GCAGCCACCA GTGGACCTAG CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG 2427
GGTCTTATCT CTCTGGGACC TAGGGGGACG GGGCTGACAT CTACATTTTT TAAAACTGAA 2487
TCTTAATCGA TGAATGTAAA CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT 2547
GACATTTACA GGAGGCCCCG GAGAAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCCAAG 2607
GATGACCACA CCCGAAGTCC TGTCACTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC 2667
CCCCGCTTAG CCCCGCTGAG CTTGGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC 2727
TGTGCCATGC CCAAGGCCTA GGTTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA 2787
ATTCGAAAAC AACCGTCCTG CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG 2847
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BNSDOCID: <EP 0633268A2>

GGGGTTCTAG AAAATATAGG TTCCTATAAT AAAATGGCAC CTTCCCCCTT TAAAAAAAAA 2907
AAAAAA 2913

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3183 base pairs

(B) TYPE: nucleic acid

(C) STRANDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULAR TYPE: cDNA to mRNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) IMMEDIATE SOURCE:

(A) LIBRARY: human fetal brain cDNA library

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..2307

(ix) FEATURE:

(A) NAME/KEY: 3'UTR

(B) LOCATION: 2308..3183

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

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ATG AGG CTG CTG CGG CGC TGG GCG TTC GCG GCT CTG CTG CTG TCG CTG      48
Met Arg Leu Leu Arg Arg Trp Ala Phe Ala Ala Leu Leu Leu Ser Leu
1               5                  10                  15

CTC CCC ACG CCC GGT CTT GGG ACC CAA GGT ccT GCT GGA GCT CTG Cga      96
Leu Pro Thr Pro Gly Leu Gly Thr Gln Gly Pro Ala Gly Ala Leu Arg
            20                  25                  30

TGG GGG GGC TTA CCC CAG CTG GGA GGC CCA GGA GCC CCT GAG GTC ACG     144
Trp Gly Gly Leu Pro Gln Leu Gly Gly Pro Gly Ala Pro Glu Val Thr
        35                  40                  45

GAA CCC AGC CGT CTG GTT AGG GAG AGC TCC GGG GGA GAG GTC CGA AAG     192
Glu Pro Ser Arg Leu Val Arg Glu Ser Ser Gly Gly Glu Val Arg Lys
    50                  55                  60

CAG CAG CTG GAC ACA AGG GTC CGC CAG GAG CCA CCA GGG GGC CCG CCT     240
Gln Gln Leu Asp Thr Arg Val Arg Gln Glu Pro Pro Gly Gly Pro Pro
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BNSDOCID: <EP 0633268A2>

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 65                  70                  75                  80
GTC CAT CTG GCC CAG GTG AGT TTC GTC ATC CCA GCC TTC AAC TCA AAC   288
Val His Leu Ala Gln Val Ser Phe Val Ile Pro Ala Phe Asn Ser Asn
                 85                  90                  95
TTC ACC CTG GAC CTG GAG CTG AAC CAC CAc CTC CTC TCC TCG CAA TAC   336
Phe Thr Leu Asp Leu Glu Leu Asn His His Leu Leu Ser Ser Gln Tyr
            100                 105                 110
GTG GAG CGC CAC TTC AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GGG   384
Val Glu Arg His Phe Ser Arg Glu Gly Thr Thr Gln His Ser Thr Gly
        115                 120                 125
GCT GGA GAC CAC TGC TAC TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC   432
Ala Gly Asp His Cys Tyr Tyr Gln Gly Lys Leu Arg Gly Asn Pro His
    130                 135                 140
TCC TTC GCC GCC CTC TCC ACC TGC CAG GGG CTG CAT GGG GTC TTC TCT   480
Ser Phe Ala Ala Leu Ser Thr Cys Gln Gly Leu His Gly Val Phe Ser
145                 150                 155                 160
GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG GTG GCT GGA CCT   528
Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu Val Ala Gly Pro
                165                 170                 175
TGG GGA GCC CCT CAG GGA CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT   576
Trp Gly Ala Pro Gln Gly Pro Leu Pro His Leu Ile Tyr Arg Thr Pro
            180                 185                 190
CTC CTC CCA GAT CCC CTC GGA TGC AGG GAA CCA GGC TGC CTG TTT GCT   624
Leu Leu Pro Asp Pro Leu Gly Cys Arg Glu Pro Gly Cys Leu Phe Ala
        195                 200                 205
GTG CCT GCC CAG TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA   672
Val Pro Ala Gln Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys
    210                 215                 220
AGG CAG GTC CGC CGG GGC CAC CCT ACA GTG CAC AGT GAA ACC AAG TAT   720
Arg Gln Val Arg Arg Gly His Pro Thr Val His Ser Glu Thr Lys Tyr
225                 230                 235                 240
GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG CTG TTC GAG CAG ATG CGA   768
Val Glu Leu Ile Val Ile Asn Asp His Gln Leu Phe Glu Gln Met Arg
                245                 250                 255
CAG TCG GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG   816
Gln Ser Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu
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                260                 265                 270
GCC GAT GTG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT    864
Ala Asp Val Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val
        275                 280                 285
GCC ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC    912
Ala Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp
    290                 295                 300
CTC CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG    960
Leu Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu
305                 310                 315                 320
CCT GAG CCC AGT AAT GCC ACC CAC CTC TTC TCG GGC AGG ACC TTC CAG   1008
Pro Glu Pro Ser Asn Ala Thr His Leu Phe Ser Gly Arg Thr Phe Gln
                325                 330                 335
AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA TGC TCC CTG TCC   1056
Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile Cys Ser Leu Ser
            340                 345                 350
CAT GGC GGG GGT GTG AAC GAG TAC GGC AAC ATG GGG GCG ATG GCC GTG   1104
His Gly Gly Gly Val Asn Glu Tyr Gly Asn Met Gly Ala Met Ala Val
        355                 360                 365
ACC CTT GCC CAG ACG CTG GGA CAG AAC CTG GGC ATG ATG TGG AAC AAA   1152
Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly Met Met Trp Asn Lys
    370                 375                 380
CAC CGG AGC TCG GCA GGG GAC TGC AAG TGT CCA GAC ATC TGG CTG GGC   1200
His Arg Ser Ser Ala Gly Asp Cys Lys Cys Pro Asp Ile Trp Leu Gly
385                 390                 395                 400
TGC ATC ATG GAG GAC ACT GGG TTC TAC CTG CCC CGC AAG TTC TCT CGC   1248
Cys Ile Met Glu Asp Thr Gly Phe Tyr Leu Pro Arg Lys Phe Ser Arg
                405                 410                 415
TGC AGC ATC GAC GAG TAC AAC CAG TTT CTG CAG GAG GGT GGT GGC AGC   1296
Cys Ser Ile Asp Glu Tyr Asn Gln Phe Leu Gln Glu Gly Gly Gly Ser
            420                 425                 430
TGC CTC TTC AAC AAG CCC CTC AAG CTC CTG GAC CCC CCA GAG TGC GGG   1344
Cys Leu Phe Asn Lys Pro Leu Lys Leu Leu Asp Pro Pro Glu Cys Gly
        435                 440                 445
AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG CAG   1392
Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val Gln
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     450                 455                 460
GAG TGC AGC CGC GCA GGT GGC AAC TGC TGC AAG AAA TGC ACC CTG ACT   1440
Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr Leu Thr
465                 470                 475                 480
CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC AAG TAC   1488
His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys Lys Tyr
                485                 490                 495
GAA CCA CGG GGT GTG TCC TGC CGA GAG GCC GTG AAC GAG TGC GAC ATC   1536
Glu Pro Arg Gly Val Ser Cys Arg Glu Ala Val Asn Glu Cys Asp Ile
            500                 505                 510
GCG GAG ACC TGC ACC GGG GAC TCT AGC CAG TGC CCG CCT AAC CTG CAC   1584
Ala Glu Thr Cys Thr Gly Asp Ser Ser Gln Cys Pro Pro Asn Leu His
        515                 520                 525
AAG CTG GAC GGT TAC TAC TGT GAC CAT GAG CAG GGC CGC TGC TAC GGA   1632
Lys Leu Asp Gly Tyr Tyr Cys Asp His Glu Gln Gly Arg Cys Tyr Gly
    530                 535                 540
GGT CGC TGC AAA ACC CGG GAC CGG CAG TGC CAG GTT CTT TGG GGC CAT   1680
Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys Gln Val Leu Trp Gly His
545                 550                 555                 560
GCG GCT GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG   1728
Ala Ala Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr
                565                 570                 575
GAG CGT GGG AGC TGT GGG CGC AAG GGA TCC GGC TGG GTC CAG TGC AGT   1776
Glu Arg Gly Ser Cys Gly Arg Lys Gly Ser Gly Trp Val Gln Cys Ser
            580                 585                 590
AAG CAG GAC GTG CTG TGT GGC TTC CTC CTC TGT GTC AAC ATC TCT GGA   1824
Lys Gln Asp Val Leu Cys Gly Phe Leu Leu Cys Val Asn Ile Ser Gly
        595                 600                 605
GCT CCT CGG CTA GGG GAC CTG GTG GGA GAC ATC AGT AGT GTC ACC TTC   1872
Ala Pro Arg Leu Gly Asp Leu Val Gly Asp Ile Ser Ser Val Thr Phe
    610                 615                 620
TAC CAC CAG GGC AAG GAG CTG GAC TGC AGG GGA GGC CAC GTG CAG CTG   1920
Tyr His Gln Gly Lys Glu Leu Asp Cys Arg Gly Gly His Val Gln Leu
625                 630                 635                 640
GCG GAC GGC TCT GAC CTG AGC TAT GTG GAG GAT GGC ACA GCC TGC GGG   1968
Ala Asp Gly Ser Asp Leu Ser Tyr Val Glu Asp Gly Thr Ala Cys Gly
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                    645                 650                 655
CCT AAC ATG TTG TGC CTG GAC CAT CGC TGC CTG CCA GCT TCT GCC TTC   2016
Pro Asn Met Leu Cys Leu Asp His Arg Cys Leu Pro Ala Ser Ala Phe
                660                 665                 670
AAC TTC AGC ACC TGC CCC GGC AGT GGG GAG CGC CGG ATT TGC TCC CAC   2064
Asn Phe Ser Thr Cys Pro Gly Ser Gly Glu Arg Arg Ile Cys Ser His
        675                 680                 685
CAC GGG GTC TGC AGC AAT GAA GGG AAG TGC ATC TGT CAG CCA GAC TGG   2112
His Gly Val Cys Ser Asn Glu Gly Lys Cys Ile Cys Gln Pro Asp Trp
    690                 695                 700
ACA GGC AAA GAC TGC AGT ATC CAT AAC CCC CTG CCC ACG TCC CCA CCC   2160
Thr Gly Lys Asp Cys Ser Ile His Asn Pro Leu Pro Thr Ser Pro Pro
705                 710                 715                 720
ACG GGG GAG ACG GAG AGA TAT AAA GGT CCC AGC GGC ACC AAC ATC ATC   2208
Thr Gly Glu Thr Glu Arg Tyr Lys Gly Pro Ser Gly Thr Asn Ile Ile
                725                 730                 735
ATT GGC TCC ATC GCT GGG GCT GTC CTG GTT GCA GCC ATC GTC CTG GGC   2256
Ile Gly Ser Ile Ala Gly Ala Val Leu Val Ala Ala Ile Val Leu Gly
            740                 745                 750
GGC ACG GGC TGG GGA TTT AAA AAC ATT CGC CGA GGA AGG TCC GGA GGG   2304
Gly Thr Gly Trp Gly Phe Lys Asn Ile Arg Arg Gly Arg Ser Gly Gly
        755                 760                 765
GCC TAAGTGCCAC CCTCCTCCCT CCAAGCCTGG CACCCACCGT CTCGGCCCTG        2357
Ala
AACCACGAGG CTGCCCCCAT CCAGCCACGG AGGGAGGCAC CATGCAAATG TCTTCCAGGT 2417
CCAAACCCTT CAACTCCTGG CTCCGCAGGG GTTTGGGTGG GGGCTGTGGC CCTGCCCTTG 2477
GCACCACCAG GGTGGACCAG GCCTGGAGGG CACTTCCTCC ACAGTCCCCC ACCCACCTCC 2537
TGCGGCTCAG CCTTGCACAC CCACTGCCCC GTGTGAATGT AGCTTCCACC TCATGGATTG 2597
CCACAGCTCA ACTCGGGGGC ACCTGGAGGG ATGCCCCCAG GCAGCCACCA GTGGACCTAG 2657
CCTGGATGGC CCCTCCTTGC AACCAGGCAG CTGAGACCAG GGTCTTATCT CTCTGGGACC 2717
TAGGGGGACG GGGCTGACAT CTACATTTTT TAAAACTGAA TCTTAATCGA TGAATGTAAA 2777
CTCGGGGGTG CTGGGGCCAG GGCAGATGTG GGGATGTTTT GACATTTACA GGAGGCCCCG 2837
GAGAAACTGA GGTATGGCCA TGCCCTAGAC CCTCCCCAAG GATGACCACA CCCGAAGTCC 2897
TGTCACTGAG CACAGTCAGG GGCTGGGCAT CCCAGCTTGC CCCCGCTTAG CCCCGCTGAG 2957
CTTGGAGGAA GTATGAGTGC TGATTCAAAC CAAAGCTGCC TGTGCCATGC CCAAGGCCTA 3017
GGTTATGGGT ACGGCAACCA CATGTCCCAG ATCGTCTCCA ATTCGAAAAC AACCGTCCTG 3077
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BNSDOCID: <EP 0633268A2>

CTGTCCCTGT CAGGACACAT GGATTTTGGC AGGGCGGGGG GGGGTTCTAG AAAATATAGG 3137

TTCCTATAAT AAAATGGCAC CTTCCCCCTT TAAAAAAAAA AAAAAA 3183

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9278 base pairs

(B) TYPE: nucleic acid

(C) STRANDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Genomic DNA

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Homo sapiens

(vii) IMMEDIATE SOURCE:

(A) LIBRARY: human DNA cosmid library

(ix) FEATURE:

(A) NAME/KEY: exon 1

(B) LOCATION: 28..44

(ix) FEATURE:

(A) NAME/KEY: exon 2

(B) LOCATION: 308..374

(ix) FEATURE:

(A) NAME/KEY: exon 3

(B) LOCATION: 909..994

(ix) FEATURE:

(A) NAME/KEY: exon 4

(B) LOCATION: 1081..1156

(ix) FEATURE:

(A) NAME/KEY: exon 5

(B) LOCATION: 1591..1657

(ix) FEATURE:

(A) NAME/KEY: exon 6

(B) LOCATION: 1725..1792

(ix) FEATURE:

(A) NAME/KEY: exon 7

(B) LOCATION: 2182..2256

(ix) FEATURE:

BNSDOCID: <EP 0633268A2>

(A) NAME/KEY: xon 8
(B) LOCATION: 2339..2410
(ix) FEATURE:
(A) NAME/KEY: exon 9
(B) LOCATION: 2588..2754
(ix) FEATURE:
(A) NAME/KEY: exon 10
(B) LOCATION: 3248..3332
(ix) FEATURE:
(A) NAME/KEY: exon 11
(B) LOCATION: 3445..3535
(ix) FEATURE:
(A) NAME/KEY: exon 12
(B) LOCATION: 3645..3696
(ix) FEATURE:
(A) NAME/KEY: exon 13
(B) LOCATION: 4014..4113
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(A) NAME/KEY: exon 14
(B) LOCATION: 4196..4267
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(A) NAME/KEY: exon 15
(B) LOCATION: 4386..4478
(ix) FEATURE:
(A) NAME/KEY: exon 16
(B) LOCATION: 4920..5000
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(A) NAME/KEY: exon 17
(B) LOCATION: 5347..5397
(ix) FEATURE:
(A) NAME/KEY: exon 18
(B) LOCATION: 5501..5564
(ix) FEATURE:
(A) NAME/KEY: exon 19
(B) LOCATION: 5767..5866
(ix) FEATURE:

BNSDOCID: <EP 0633268A2>

(A) NAME/KEY: exon 20
(B) LOCATION: 6073..6202
(ix) FEATURE:
(A) NAME/KEY: exon 21
(B) LOCATION: 6300..6468
(ix) FEATURE:
(A) NAME/KEY: exon 22
(B) LOCATION: 6557..6671
(ix) FEATURE:
(A) NAME/KEY: exon 23
(B) LOCATION: 6756..6846
(ix) FEATURE:
(A) NAME/KEY: exon 24
(B) LOCATION: 7829..7846
(ix) FEATURE:
(A) NAME/KEY: exon 25
(B) LOCATION: 8165..9038
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9

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GCGTTTACTG GCAAACCGCA TTTGTAA  ATG TGC TGG CTG AGC CA NNNNNNNNNN    54
                               Met Cys Trp Leu Ser His
                               1               5
NNNNCCAGGT GAGTTTCGTC ATCCAGCCTT CAACTCAAAC TTCACCCTGG ACCTGGAGCT  114
GAACCAGTGA GNGTGGCCTT GAGCCCAAGA GGAAGGGCAG TGGTGGNNNG GGGGAGACAT  174
GGCTAGGGCC TGGCTGCTGG GGGTCTGGGG GTTGGGCCTG GCGAGAGGGG ACCTGGGTCC  234
TGACCTGAGG CGAGCCTAAA GCCCGACCTC ACCTCGCCCG TGACCCCCCT TCCTGCTGCC  294
CCCTCTGTCT CAG C CAA CTC  CTC TCC TCG CAA TAC GTG GAG CGC CAC TTC  344
                 Gln Leu  Leu Ser Ser Gln Tyr Val Glu Arg His Phe
                          10                  15
AGC CGG GAG GGG ACA ACC CAG CAC AGC ACC GTGAGTGCCA CTGCTGGGGA      394
Ser Arg Glu Gly Thr Thr Gln His Ser Thr
    20                  25
CCGGGGCCGG GGATGGAAGG GAGGTGCTGT TTCTGTGGTT CTGTGGTCAC AGGTGTAGGG  454
ACAGGTGGCC ACTGGAGATG GGGTCCTGGG CCTGGCCCCT CAGCACCTTC CCTCTCTCCC  514
GACCCAGGAG GCTCTGAGGG TGGACAGTGG GCAGCTTAGT GCATAGGGCC CTGAAGTCCC  574
CTCACTTGGC CCCAGAGCTC TGACCCCCAG CCAGCCCACG TGGGGCCTAC AGGGACACTC  634
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BNSDOCID: <EP 0633268A2>

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AGGTTCCTAA CCCCAGAGGG CTAGGAACTT GCCCAGGGTG GCACGGCAAA TTAGGAGCAC  754
CAGCCATCTA GAAACAGGCT CCAGAGCCCC AGGNATACCC AGGGATNGTG GCCACCTGCA  814
CACAGGGCAG CTTCAGTGTC CCCCAAAAAG CCTTGAGGCC CATTGGCTGC CCCCGGCCTC  874
ATGCCAGCGT TCTGCTCACT GTTCTGCTCC TTAG GGG GCT GGA GAC CAC TGC TAC  929
                                       Gly Ala Gly Asp His Cys Tyr
                                           30                  35
TAC CAG GGG AAG CTC CGG GGG AAC CCG CAC TCC TTC GCC GCC CTC TCC    977
Tyr Gln Gly Lys Leu Arg Gly Asn Pro His Ser Phe Ala Ala Leu Ser
                40                  45                  50
ACC TGC CAG GGG CTG CA GTGAGTATGG GGAGGGGCCG GGCAGCTGGG           1024
Thr Cys Gln Gly Leu His
            55
AGAAGCCTCT GGCCCAGGCC TGGGGACGGA GGGGAGCTGC GCCTCTCTCT CCACAG T   1081
GGG GTC TTC TCT GAT GGG AAC TTG ACT TAC ATC GTG GAG CCC CAA GAG   1129
Gly Val Phe Ser Asp Gly Asn Leu Thr Tyr Ile Val Glu Pro Gln Glu
        60                  65                  70
GTG GCT GGA CCT TGG GGA GCC CCT CAG GTAAGCCCCA CACAACCCCT         1176
Val Ala Gly Pro Trp Gly Ala Pro Gln
    75                  80
TGCCATCCTC TCTGGTGGCC CTGCCAAGCT TGTCCCAACA GCTGTTGCTG CCACCTCTTC 1236
CTCCTCCGGC TCCTCCCTCA GTAACCCCAG CCTCACTGCC CTCTTCAGTG ACCCCAGCTC 1396
TGGTTCCCTC CCTCCTGTGC CCCAGCTCCC CCTGTGCCCC CAGCTCCAAT GTCCCATCTG 1356
TCCCATAAGT GACCTCCCAT TGGGCTCCAA TGTCCTTTGC CCCTGTCTCT CAGGGTGCCC 1416
CCAGGTCTTG ACCCCGGAAT CTGAGCATCT GGGAGATCAG ATCCGACATG GGAGCTGTGG 1476
CCAGTTCTGG GTCACCCCAG GGTGGGGTGG AGGCGAGGGC TGGATCTGGC CCCCGCCAAG 1536
TGGCCTGGAG CAGGCCCAGT TGGCACCCCA AGAACTAATT TCCCCTCATT GCAG GGA   1593
                                                            Gly
CCC CTT CCC CAC CTC ATT TAC CGG ACC CCT CTC CTC CCA GAT CCC CTC   1641
Pro Leu Pro His Leu Ile Tyr Arg Thr Pro Leu Leu Pro Asp Pro Leu
    85                  90                  95
GGA TGC AGG GAA CCA G GTAAGGGAGG GGAGGGGGGG TGGGGAGGGG CCNGGCTGTG 1697
Gly Cys Arg Glu Pro Gly
    100
CCCCCCTCAC CTGCCCCTCC CCGACAG GC TGC CTG TTT GCT GTG CCT GCC CAG  1750
                                   Cys Leu Phe Ala Val Pro Ala Gln
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BNSDOCID: <EP 0633268A2>

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                                        105                 110
TCG GCT CCT CCA AAC CGG CCG AGG CTG AGA AGG AAA AGG CAG                 1792
Ser Ala Pro Pro Asn Arg Pro Arg Leu Arg Arg Lys Arg Gln
    115                 120                 125
GTACGGGGGC CCGCACAGAC CTCGGGCTGC AGAGACCTCG GGCTGCAGAG AGACCTCGGC 1852
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CTGATTCCAA GTGCCCACCC ACCCCCCAG GTC CGC CGG GGC CAC CCT ACA GTG    2205
                                Val Arg Arg Gly His Pro Thr Val
                                        130                 135
CAC AGT GAA ACC AAG TAT GTG GAG CTA ATT GTG ATC AAC GAC CAC CAG    2253
His Ser Glu Thr Lys Tyr Val Glu Leu Ile Val Ile Asn Asp His Gln
            140                 145                 150
CTG GTGAGTGCCA GGGCAGGGAC AGGGCGTGAC ACTGGGAGGC CCCTGAGGAG         2306
Leu
CCTGGCCCTC CTCCCATTCT TCTCTCTCCC AG TTC GAG CAG ATG CGA CAG TCG    2359
                                Phe Glu Gln Met Arg Gln Ser
                                        155
GTG GTC CTC ACC AGC AAC TTT GCC AAG TCC GTG GTG AAC CTG GCC GAT    2407
Val Val Leu Thr Ser Asn Phe Ala Lys Ser Val Val Asn Leu Ala Asp
160                 165                 170                 175
GTG GTAAGCAGCT CTCCCTCCCT CCCTTCCCTC CTCCTCATGC CCCCCCACCC         2460
Val
CACCACACAC ATTAGGGGGC ACTGTCAGCC CCTGGCTCCC ACTTCCTGGA GAGAACAGAC 2520
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TCCCCAG ATA TAC AAG GAG CAG CTC AAC ACT CGC ATC GTC CTG GTT GCC    2629
        Ile Tyr Lys Glu Gln Leu Asn Thr Arg Ile Val Leu Val Ala
                    180                 185                 190
ATG GAA ACA TGG GCA GAT GGG GAC AAG ATC CAG GTG CAG GAT GAC CTC    2677
Met Glu Thr Trp Ala Asp Gly Asp Lys Ile Gln Val Gln Asp Asp Leu
                195                 200                 205
CTG GAG ACC CTG GCC CGG CTC ATG GTC TAC CGA CGG GAG GGT CTG CCT    2725
Leu Glu Thr Leu Ala Arg Leu Met Val Tyr Arg Arg Glu Gly Leu Pro
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Glu Pro Ser Asn Ala Thr His Leu Phe Ser
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CGGGGAGCCA CAGGGGAGGG CAGAAGCCAT CCTGACAGCG CACTCCCTTC CAG G GGC  3251
                                                            Gly
AGG ACC TTC CAG AGC ACG AGC AGC GGG GCA GCC TAC GTG GGG GGC ATA    3299
Arg Thr Phe Gln Ser Thr Ser Ser Gly Ala Ala Tyr Val Gly Gly Ile
    235                 240                 245
TGC TCC CTG TCC CAT GGC GGG GGT GTG AAC GAG GTGAGCAGTG             3342
Cys Ser Leu Ser His Gly Gly Gly Val Asn Glu
250                 255                 260
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TGGAAGATGT AGACATCTGT GCCCCATCTT CCCCACCCCC AG TAC GGC AAC ATG     3456
                                              Tyr Gly Asn Met
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Gly Ala Met Ala Val Thr Leu Ala Gln Thr Leu Gly Gln Asn Leu Gly
265                 270                 275                 280
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Met Met Trp Asn Lys His Arg Ser Ser Ala Gly
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CCGTGTGGCC CAGCAGCTCT GGAACGGGAG GGTGACAGTG GGAGGGGTGG TCCTTGGCCT 3615
CCCTCATATC CGCCTGGCTC ACCCCTCAG GG GAC TGC AAG TGT CCA GAC ATC     3667
                                    Asp Cys Lys Cys Pro Asp Ile
                                                        295
TGG CTG GGC TGC ATC ATG GAG GAC ACT GG GTGAGTTCTT GGGGACAACC       3716
Trp Leu Gly Cys Ile Met Glu Asp Thr Gly
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TTC TAC CTG CCC CGC AAG TTC TCT CGC TGC AGC ATC GAC GAG TAC AAC   4062
Phe Tyr Leu Pro Arg Lys Phe Ser Arg Cys Ser Ile Asp Glu Tyr Asn
    310                 315                 320
CAG TTT CTG CAG GAG GGT GGT GGC AGC TGC CTC TTC AAC AAG CCC CTC   4110
Gln Phe Leu Gln Glu Gly Gly Gly Ser Cys Leu Phe Asn Lys Pro Leu
325                 330                 335                 340
AAG GTACCAGCCC CGCGGCGGGG AGCATGGGAG CGGGCCCTGG GCGGGGTCCG       4163
Lys
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                                    Leu Leu Asp Pro Pro Glu Cys
                                                345
GGG AAC GGC TTC GTG GAG GCA GGG GAG GAG TGC GAC TGC GGC TCG GTG   4264
Gly Asn Gly Phe Val Glu Ala Gly Glu Glu Cys Asp Cys Gly Ser Val
    350                 355                 360
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Gln
365
ACCAGGGAGC GTCTGAGTGG GAGGATTAGG GCTCGCCCGC CTCCTTCCCC TCCTCCCGCG 4377
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         Glu Cys Ser Arg Ala Gly Gly Asn Cys Cys Lys Lys Cys Thr
                        370                 375
CTG ACT CAC GAC GCC ATG TGC AGC GAC GGG CTC TGC TGT CGC CGC TGC   4475
Leu Thr His Asp Ala Met Cys Ser Asp Gly Leu Cys Cys Arg Arg Cys
380                 385                 390                 395
AAG GTAAGCAGGA CCGGCCGGGA GGCGGGGCCA GGACGCAGGA GGAGCGATTG       4528
Lys
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Cys Arg Glu Ala Val Asn Glu Cys Asp Ile Ala Glu Thr Cys Thr Gly
    405                 410                 415
GAC TCT AGC CAG GTCCGCCCGG CCCCGCCGTC TTGTGGAGCC CTGGGCGAGG       5040
Asp Ser Ser Gln
420
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       Cys Pro Pro Asn Leu His Lys Leu Asp Gly Tyr Tyr Cys Asp
           425                 430                 435
CAT GAG CAG GTATGATGGC TGCCCCCTGA GCCTGGGATT CAGGGCAGTC           5437
His Glu Gln
        440
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    Gly Arg Cys Tyr Gly Gly Arg Cys Lys Thr Arg Asp Arg Gln Cys
                    445                 450                 455
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Gln Val Leu Trp Gly His Ala
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                                                              Ala
GCT GAT CGC TTC TGC TAC GAG AAG CTG AAT GTG GAG GGG ACG GAG CGT   5819
Ala Asp Arg Phe Cys Tyr Glu Lys Leu Asn Val Glu Gly Thr Glu Arg
    465                 470                 475
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AAACTTGGGG CTCACTGTCT CTATAT G CCC CAA CAG GGA CGT GCT GTG TGG    6097
                              Pro Gln Gln Gly Arg Ala Val Trp
                                                  500
CTT CCT CCT CTG TGT CAA CAT CTC TGG AGC TCC TCG GCT AGG GGA CCT   6145
Leu Pro Pro Leu Cys Gln His Leu Trp Ser Ser Ser Ala Arg Gly Pro
    505                 510                 515
GGT GGG AGA CAT CAG TAGTGTCACC TTCTACCACC AGGGCAAGGA GCTGGACTGC   6200
Gly Gly Arg His Gln
520
AGGTGCTGAC CAGCACCAAA ACTCAGGGAG GGGACCTGGC AGCTGTGCTG GGGGTTAGAA 6260
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(2) INFORMATION FOR SEQ ID NO: 10:

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(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GCACCTGCCC CGGCAGT 17

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CCAGGACAGC CCCAGCGATG 20

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid

BNSDOCID: <EP 0633268A2>

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GGCTGCTGAT CGCTTCTGCT AC 22

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

GAGAAGCTGA ATGTGGAGGG 20

(2) INFORMATION FOR SEQ ID NO: 14:

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

BNSDOCID: <EP 0633268A2>

(iii) ANTI-SENSE: YES

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(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

BNSDOCID: <EP 0633268A2>

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

GATGTAAGTC AAGTTCCCAT CAGAGA 26

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

AACAGCTGGT GGTCGTTGAT CACAA 25

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

BNSDOCID: <EP 0633268A2>

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

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(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CACAGATCTG GGGGCATATG CTCCCTG 27

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

AACAAGCTTC TACTGATGTC TCCCACC 27

BNSDOCID: <EP 0633268A2>

Claims

1. An MDC protein which comprises the whole or part of the protein represented by SEQ ID NO:1, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:1.

2. The MDC protein as claimed in claim 1, which comprises the whole or part of the protein represented by SEQ ID NO:2, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:2.

3. The MDC protein as claimed in claim 1, which comprises the whole or part of the protein represented by SEQ ID NO:3, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:3.

4. The MDC protein as claimed in claim 1, which comprises the whole or part of the protein represented by SEQ ID NO:4, or which consists of a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:4.

5. The MDC protein as claimed in any of the claims 1 to 4, comprising a polypeptide having an amino acid sequence consisting of continuous at least 3 to 5 amino acids, at least 8 to 10 amino acids, at least 11 to 20 amino acids, or more than 20 amino acids in the sequence represented by the SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4.

6. The MDC protein as claimed in any of the claims 1 to 5 comprising a protein substantially equivalent to one comprising the whole or part of the protein represented by SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, or SEQ ID NO:4, wherein one or more amino acids have been replaced, deleted and/or inserted, but still producing an equal effect in research and diagnosing.

7. The MDC protein as claimed in claim 1, which comprises a polypeptide having an amino acid sequence consisting of continuous, at least eight amino acids in the sequence represented by the SEQ ID NO:1.

8. A DNA encoding the MDC protein as claimed in claim 1, which comprises the whole or part of the DNA represented by SEQ ID NO:5, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:5.

9. The DNA as claimed in claim 8, which comprises the whole or part of the DNA represented by SEQ ID NO:6, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:6.

10. The DNA as claimed in claim 8, which comprises the whole or part of the DNA represented by SEQ ID NO:7, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:7.

11. The DNA as claimed in claim 8, which comprises the whole or part of the DNA represented by SEQ ID NO:8, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:8.

12. The DNA as claimed in any of the claims 8 to 11, comprising a DNA sequence consisting of at least 6 bases, at least 8 bases, at least 10 to 12 bases or about 15 to 25 bases.

13. A DNA which comprises the whole or part of the DNA represented by SEQ ID NO:9 including exons and introns therein, or which consists of a DNA substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:9 including exons and introns therein.

14. The DNA as claimed in any of the claims 8 to 13, comprising a DNA sequence substantially equivalent to one comprising the whole or part of the DNA represented by SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9, wherein one or more bases have been replaced, deleted and/or

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inserted, but still producing an equal effect in gene analysis and diagnosis.

15. A plasmid containing the DNA as claimed in claim 8.

16. A plasmid containing the DNA as claimed in claim 13.

17. A transformant carrying the plasmid as claimed in claim 15.

18. A transformant carrying the plasmid as claimed in claim 16.

19. A process for the production of the MDC protein as claimed in claim 1, which comprises the steps of culturing the transformant as claimed in claim 17 and collecting the resulting expression product.

20. A process for the production of the MDC protein as claimed in claim 1, which comprises the steps of culturing the transformant as claimed in claim 18 and collecting the resulting expression product.

21. An antibody combinable to the MDC protein as claimed in claim 1.

22. A primer or probe which has a DNA sequence, comprising a part of the DNA sequence of the DNA as claimed in claim 8, or a DNA sequence complementary to a part of the DNA sequence of the DNA as claimed in claim 8.

23. The primer or probe as claimed in claim 22, wherein the part of the DNA sequence consists of at least six bases.

24. A primer or probe which has a DNA sequence, comprising a part of the DNA sequence of the DNA as claimed in claim 13, or a DNA sequence complementary to a part of the DNA sequence of the DNA as claimed in claim 13.

25. The primer or probe as claimed in claim 24, wherein the part of the DNA sequence consists of at least six bases.

26. A gene analysis method which comprises the step of hybridizing the primer or probe as claimed in claim 22 to a DNA to be tested.

27. A gene analysis method which comprises the step of hybridizing the primer or probe as claimed in claim 24 to a DNA to be tested.

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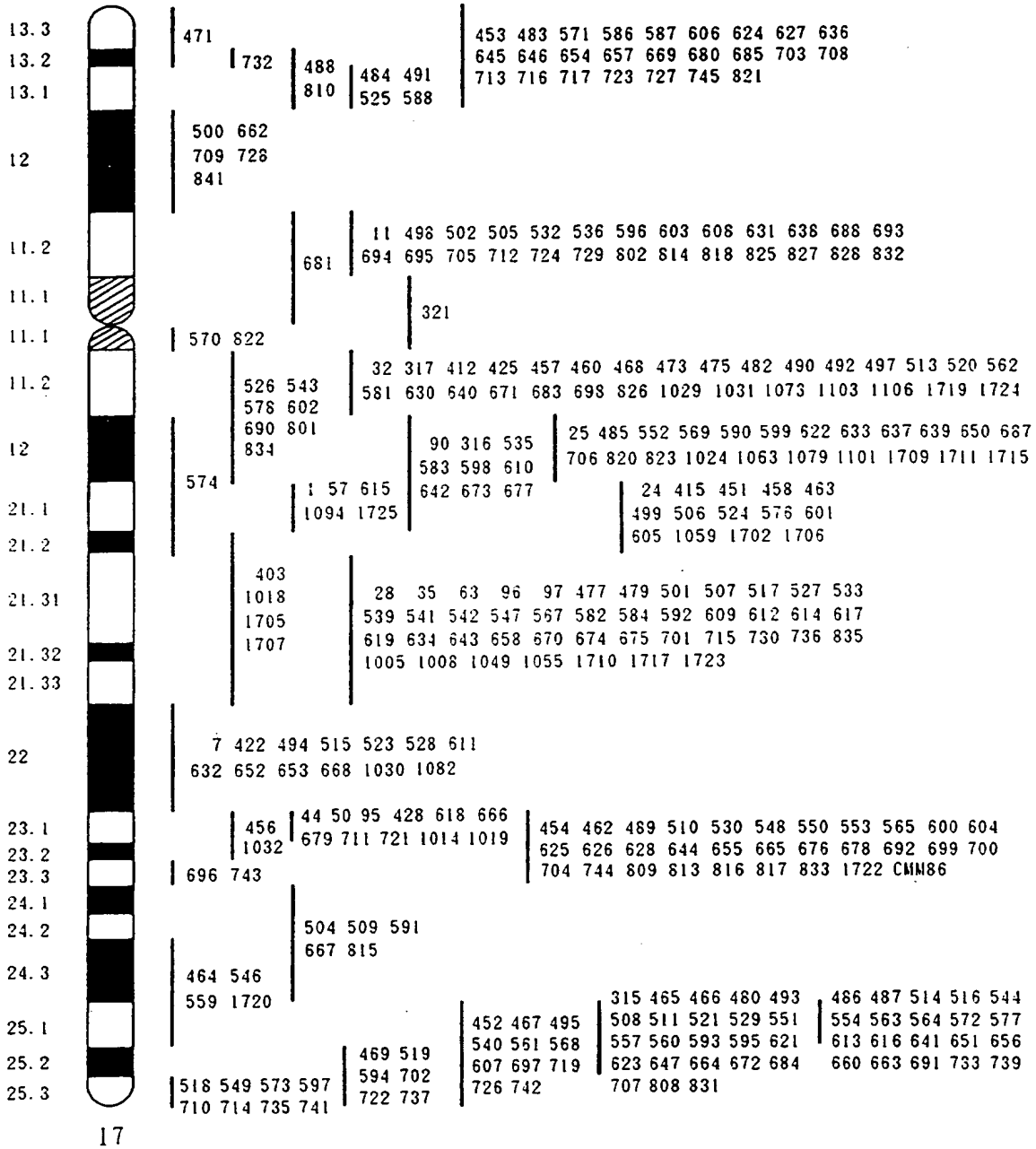
FIG. 1


13.3
13.2
13.1
12
11.2
11.1
11.1
11.2
12
21.1
21.2
21.31
21.32
21.33
22
23.1
23.2
23.3
24.1
24.2
24.3
25.1
25.2
25.3
17
471
732
488
810
484 491
525 588
453 483 571 586 587 606 624 627 636
645 646 654 657 669 680 685 703 708
713 716 717 723 727 745 821
500 662
709 728
841
681
11 498 502 505 532 536 596 603 608 631 638 688 693
694 695 705 712 724 729 802 814 818 825 827 828 832
321
570 822
526 543
578 602
690 801
834
32 317 412 425 457 460 468 473 475 482 490 492 497 513 520 562
581 630 640 671 683 698 826 1029 1031 1073 1103 1106 1719 1724
90 316 535
583 598 610
642 673 677
25 485 552 569 590 599 622 633 637 639 650 687
706 820 823 1024 1063 1079 1101 1709 1711 1715
574
1 57 615
1094 1725
24 415 451 458 463
499 506 524 576 601
605 1059 1702 1706
403
1018
1705
1707
28 35 63 96 97 477 479 501 507 517 527 533
539 541 542 547 567 582 584 592 609 612 614 617
619 634 643 658 670 674 675 701 715 730 736 835
1005 1008 1049 1055 1710 1717 1723
7 422 494 515 523 528 611
632 652 653 668 1030 1082
456
1032
44 50 95 428 618 666
679 711 721 1014 1019
454 462 489 510 530 548 550 553 565 600 604
625 626 628 644 655 665 676 678 692 699 700
704 744 809 813 816 817 833 1722 CMM86
696 743
504 509 591
667 815
464 546
559 1720
452 467 495
540 561 568
607 697 719
726 742
315 465 466 480 493
508 511 521 529 551
557 560 593 595 621
623 647 664 672 684
707 808 831
486 487 514 516 544
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469 519
594 702
722 737
518 549 573 597
710 714 735 741

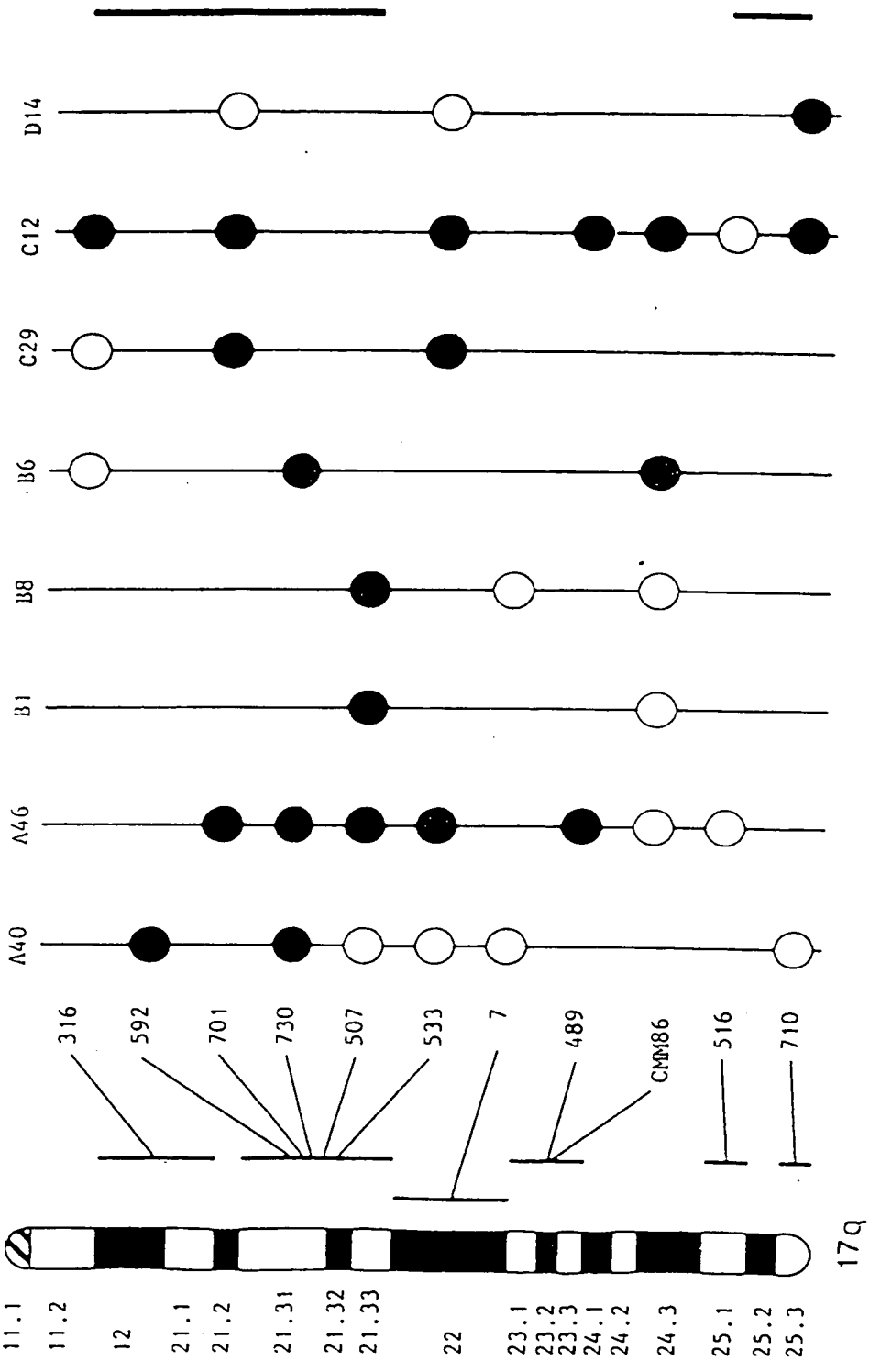
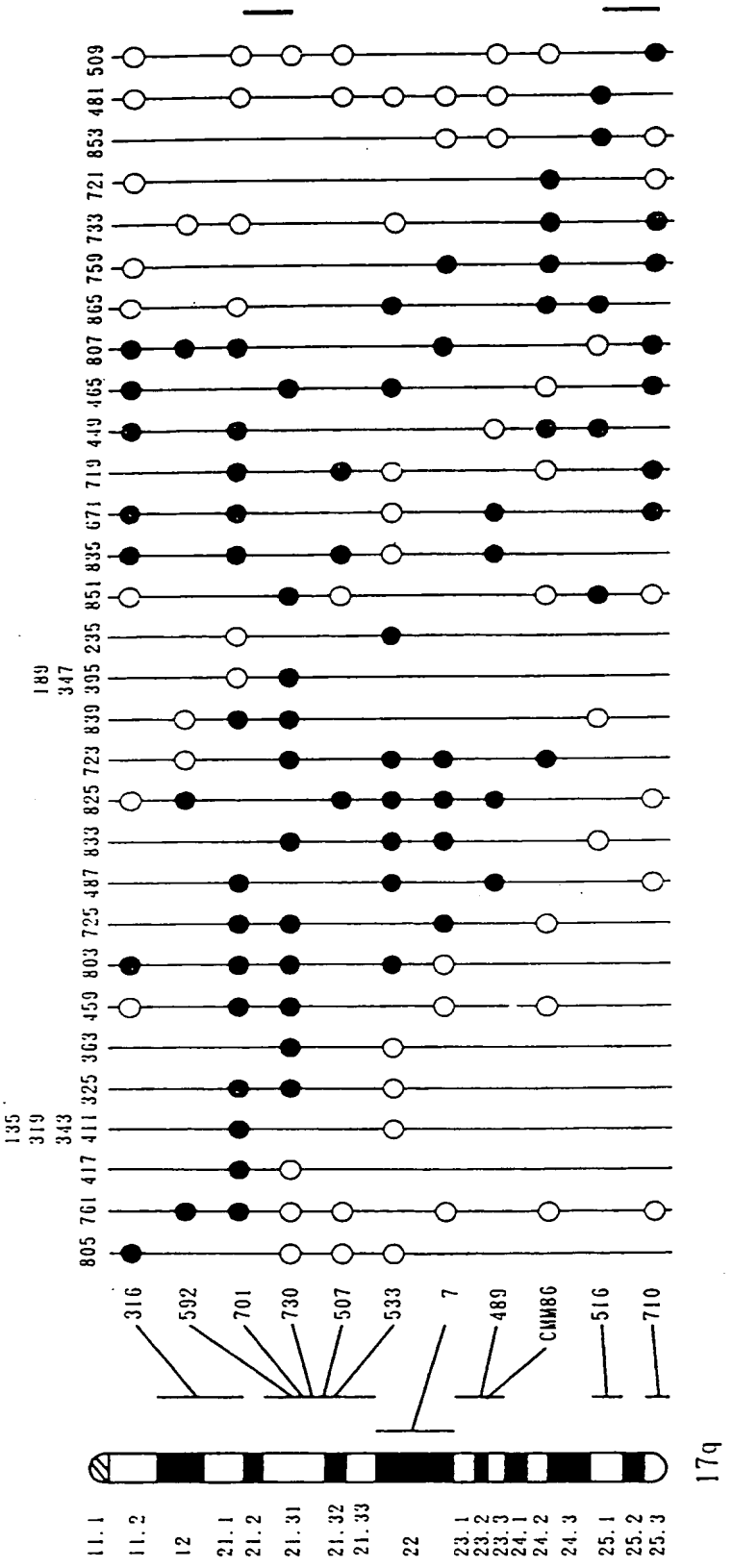

D14
C12
C29
B6
B8
B1
A46
A40
316
592
701
730
507
533
7
489
CMM86
516
710
11.1
11.2
12
21.1
21.2
21.31
21.32
21.33
22
23.1
23.2
23.3
24.1
24.2
24.3
25.1
25.2
25.3
17q

FIG. 2

FIG. 3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135 319 343
316 592 701 730 507 533 7 489 CHM86 516 710
11.1 11.2 12 21.1 21.2 21.31 21.32 21.33 22 23.1 23.2 23.3 24.1 24.2 24.3 25.1 25.2 25.3
17q

FIG. 4

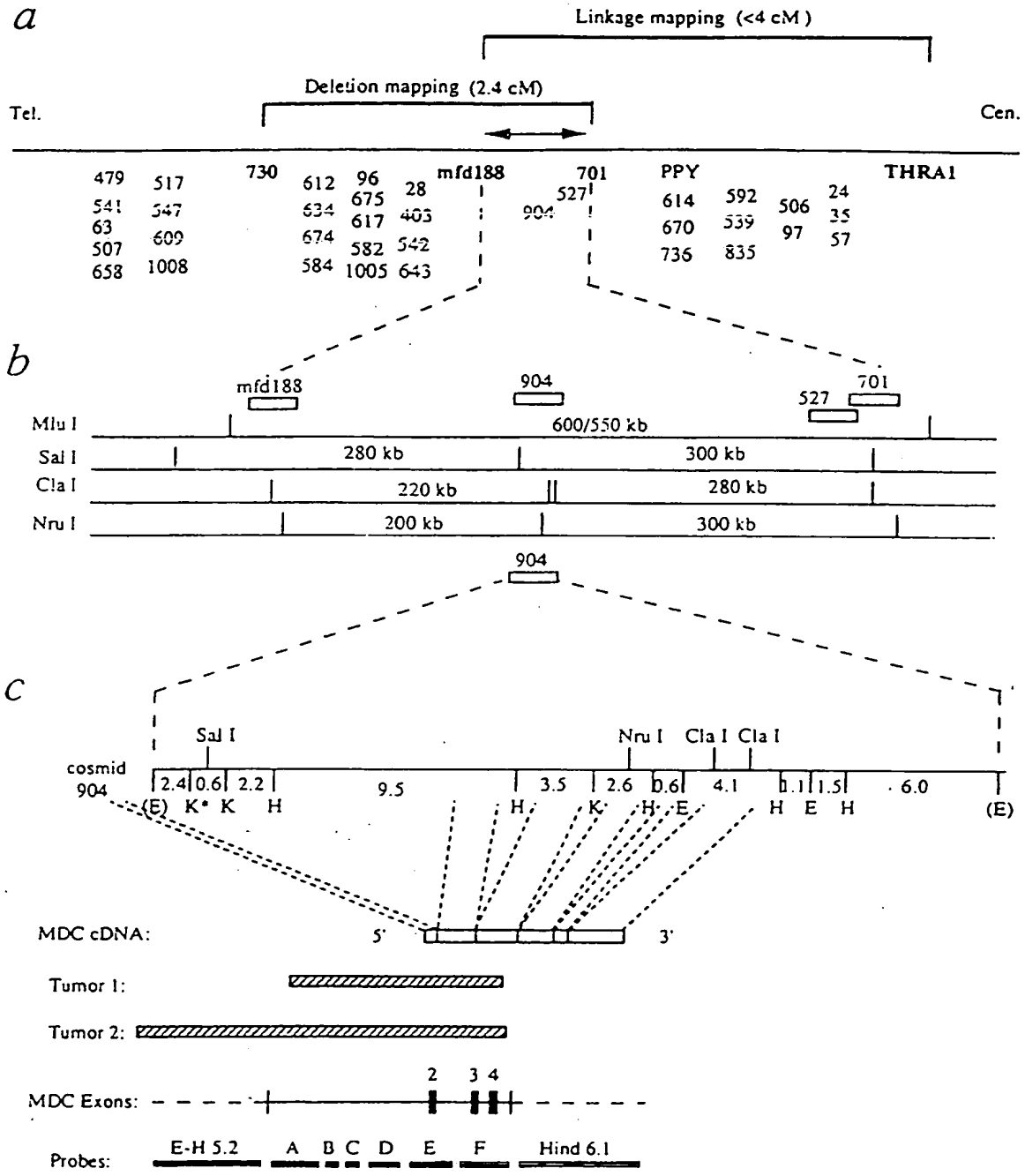
a
Linkage mapping (<4 cM)
Deletion mapping (2.4 cM)
Tel.
Cen.
mfd188
701
PPY
THRA1
b
mfd188
904
527
701
Mlu I
600/550 kb
Sal I
280 kb
300 kb
Cla I
220 kb
280 kb
Nru I
200 kb
300 kb
c
Sal I
Nru I
Cla I
Cla I
cosmid 904
MDC cDNA:
5'
3'
Tumor 1:
Tumor 2:
MDC Exons:
Probes:
E-H 5.2
A
B
C
D
E
F
Hind 6.1

FIG. 5

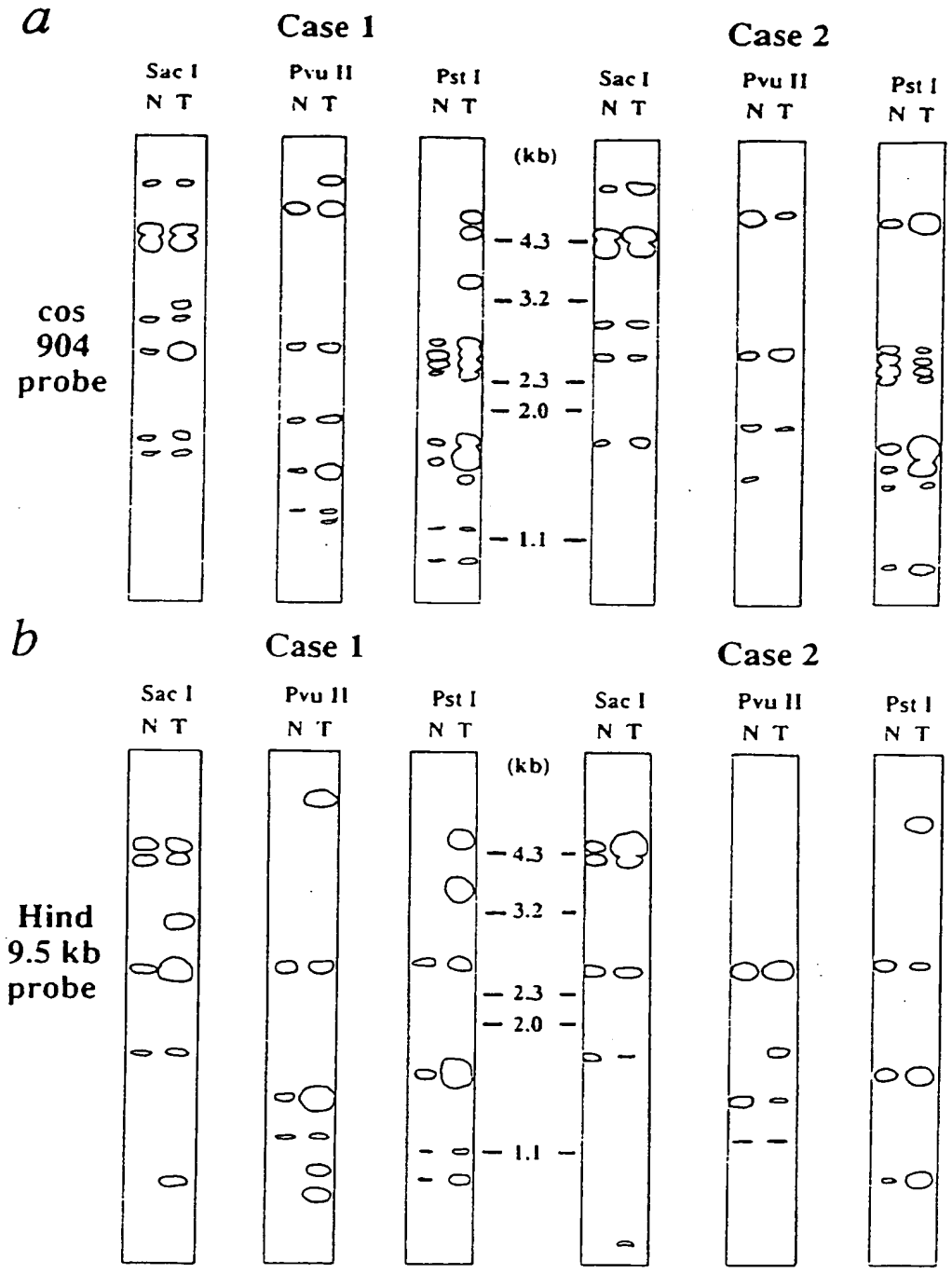

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FIG. 6

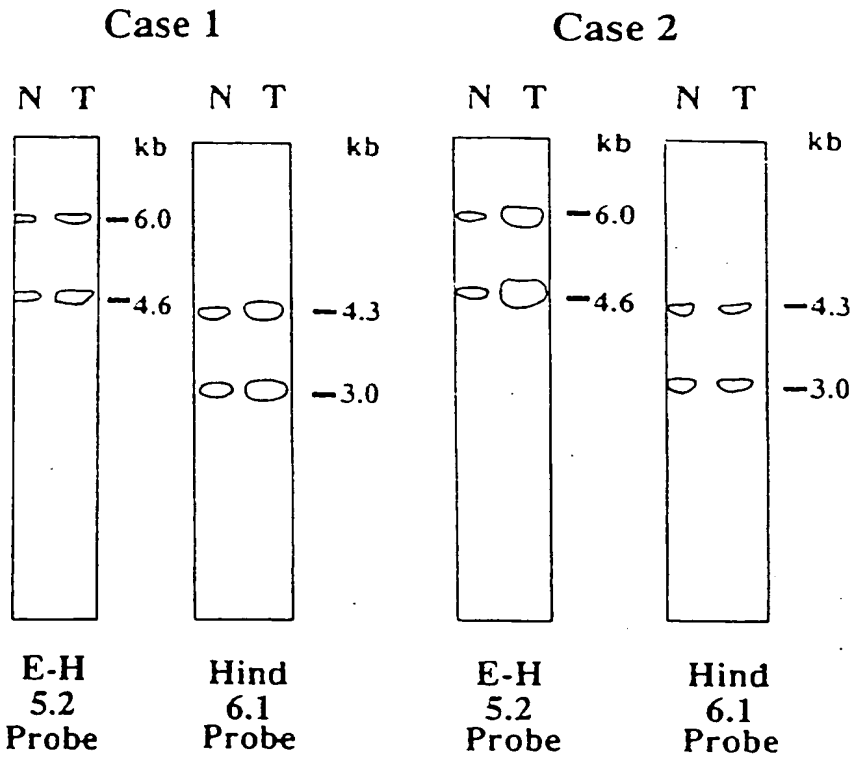

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FIG. 7

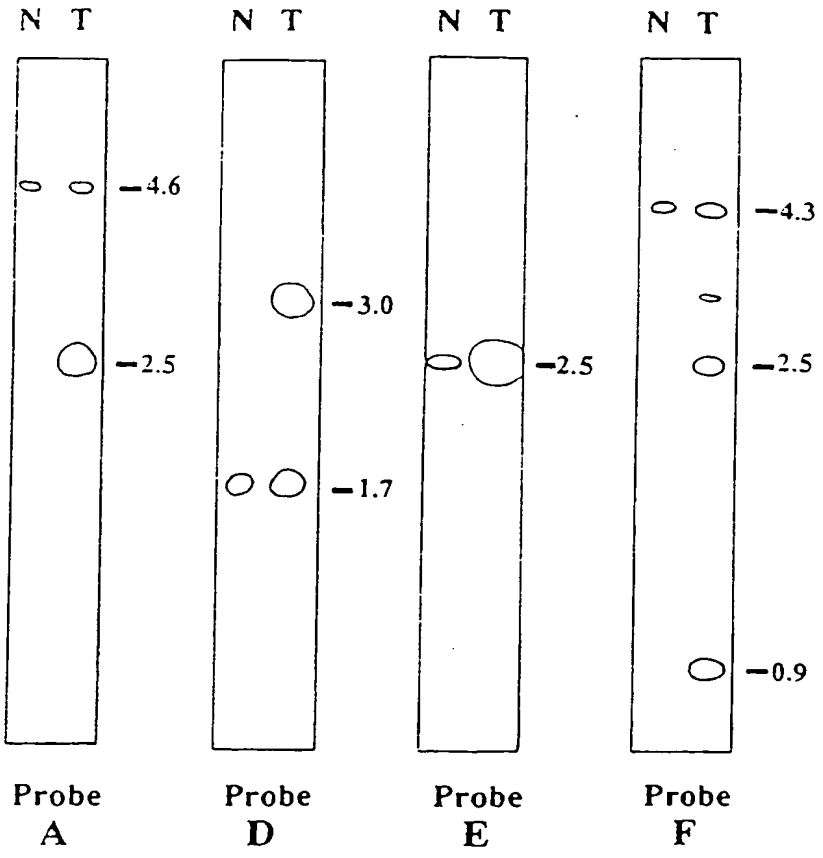

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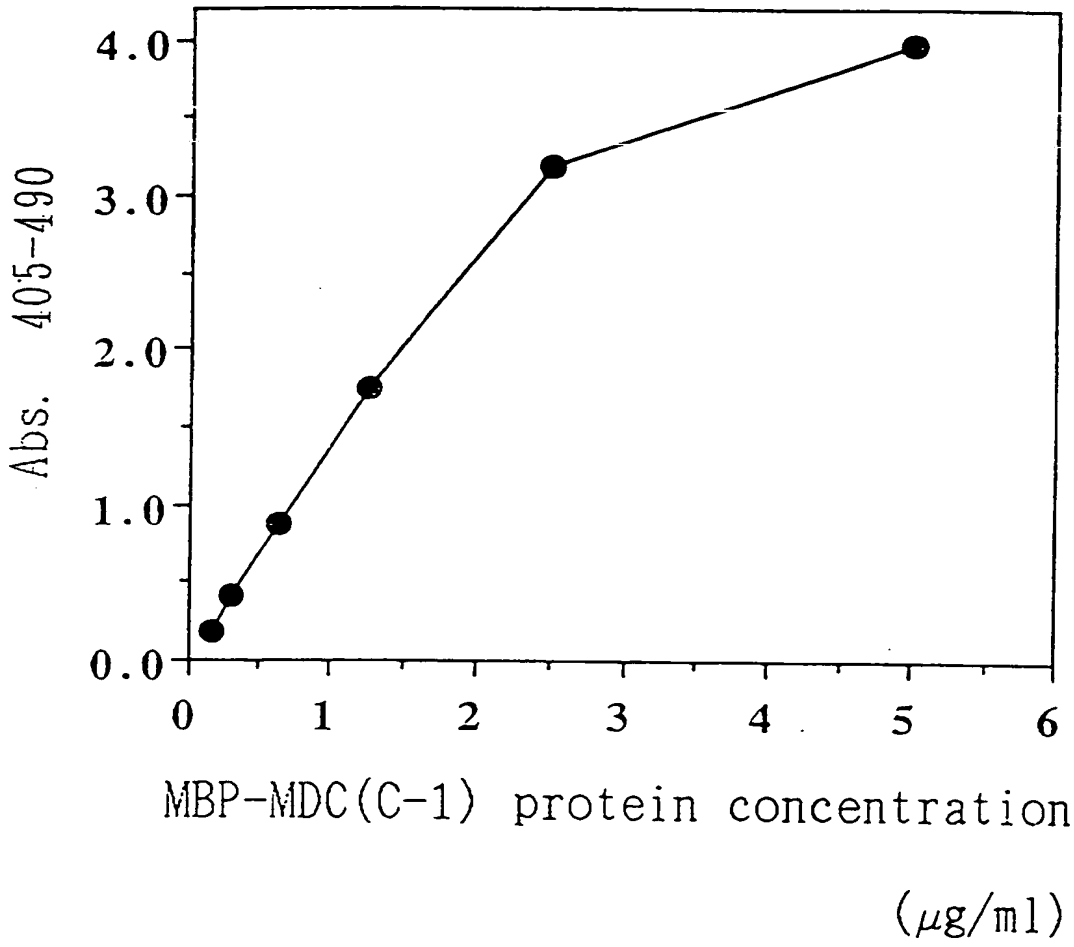
FIG. 8


4.0
3.0
2.0
1.0
0.0
Abs. 405-490
0
1
2
3
4
5
6
MBP-MDC(C-1) protein concentration
(μg/ml)

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Office européen des brevets

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Arabellastrasse 4
81925 München (DE)

(54) MDC proteins and DNAs encoding the same

(57) The present invention provide a gene present in a commonly deleted region of a chromosome in breast and ovarian cancers and encoding a novel protein, the protein ("MDC protein") encoded by the gene, a method for the diagnosis of cancer by using an antibody combinable to the protein, and others.

A detailed genetic map of human chromosome 17 was constructed to analyze the chromosome in breast and ovarian cancer tissues, and a gene encoding a novel protein was cloned and its structure was determined. As a result of gene analysis using DNA probes derived from the gene, a gene mutation was confirmed in breast cancer tissues. Moreover, a transformant carrying a plasmid containing the gene was grown to obtain the MDC protein. Furthermore, a monoclonal antibody was prepared by using the protein as antigen.

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2.14.16/3.4

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EUROPEAN SEARCH REPORT

Application Number
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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 27, 25 September 1990, MD US, pages 16068-16073, XP002036612 H.TAKEYA ET AL.: "The complete amino acid sequence of the high molecular mass hemorrhagic protein HR1B isolated from the venom of Trimeresurus flavoviridis" * figure 2 * ---	1-7	C07K14/47 C12N15/12 C07K16/18 C12Q1/68 G01N33/574
X	JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 268, no. 2, 15 January 1993, MD US, pages 1058-1065, XP000336706 R.M.SCARBOROUGH ET AL.: "Characterization of the integrin specificities of disintegrins isolated from American pit viper venoms" * table II * ---	1-7	
A	EP 0 518 650 A (THE JOHN HOPKINS UNIVERSITY; PHARMAGENICS, INC.) 16 December 1992 *SEQ.ID. NO:1 and 2; figure 10a and 10b* ---	1-27	TECHNICAL FIELDS SEARCHED (Int.Cl.5) C07K C12N
P,X	NATURE GENETICS, vol. 5, no. 2, October 1993, pages 151-157, XP002036047 M.EMI ET AL.: "A novel metalloprotease/disintegrin-like gene at 17q21.3 is somatically rearranged in two primary breast cancers" * the whole document * ---	1-27	

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	31 July 1997	Cupido, M

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Application Number
EP 94 10 7487

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P,X	CANCER RESEARCH, vol. 53, 15 July 1993, MD US, pages 3382-3385, XP002036048 H.SAITO ET AL.: "Detailed deletion mapping of chromosome 17q in ovarian and breast cancers:2-cM region on 17q21.3 is often and commonly deleted in tumors" * the whole document *	8-14	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

The present search report has been drawn up for all claims

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